This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

+ *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.

+ *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.

+ *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.

+ *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at `http://books.google.com/`

EXCHANGE

SIGILLVM · VNIVERSITATIS · CALIFORNIENSIS
FIAT LVX
MDCCCLXVIII

EX LIBRIS

BIOLOGY
LIBRARY
G

COLLECTED PAPERS BY THE STAFF

of

St. Mary's Hospital
Mayo Clinic

Rochester, Minnesota

v. 4

1912

PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY
1913

BIOLOGY
LIBRARY
G

Copyright, 1913, by W. B. Saunders Company

PRINTED IN AMERICA

UNIV. OF
CALIFORNIA

FOREWORD

The sixth volume of Collected Papers by the staff of the Mayo Clinic contains the articles written and presented for publication to the various medical journals during the year 1912. This is a slight deviation from the plan adopted for the arrangement of the Collected Papers for the 1911 volume, which included only articles either read or published during that year. The present plan brings the annual volume more nearly up to date, and is the one which will be adhered to in the future.

Mrs. M. H. Mellish,
Editor.

Rochester, Minnesota,
June, 1913.

311387

LIST OF CONTRIBUTORS

ALEXANDER ARCHIBALD, M.D.
DONALD C. BALFOUR, M.B. (TOR.)
E. H. BECKMAN, B.S., M.D.
J. M. BLACKFORD, M.D.
WILLIAM F. BRAASCH, B.S., M.D.
JOHN WILLIAM DRAPER, M.D.
GEORGE B. EUSTERMAN, M.D.
H. Z. GIFFIN, B.S., M.D.
GERTRUDE BOOKER GRANGER, M.D.
M. S. HENDERSON, M.B. (TOR.)
E. S. JUDD, M.D.
WILLIAM CARPENTER MACCARTY, B.S., M.S., M.D.
JUSTUS MATTHEWS, M.D.
CHARLES H. MAYO, A.M., M.D., LL.D.
WILLIAM J. MAYO, A.M., M.D., F.R.C.S., D.SC., LL.D.
BERNARD FRANCIS MCGRATH, M.D.
H. S. PLUMMER, M.D.
A. H. SANFORD, M.D.
W. E. SISTRUNK, M.D.
FRANK SMITHIES, M.D.
LEDA J. STACY, M.D.
G. J. THOMAS, M.D.
LOUIS BLANCHARD WILSON, M.D.

MRS. M. H. MELLISH, Editor

CONTENTS

ALIMENTARY CANAL

PAGE
DIFFUSE DILATATION OF THE ESOPHAGUS WITHOUT ANATOMIC STENOSIS (CARDIOSPASM) 3
NOTES ON THE DYSPEPSIAS. WITH SPECIAL REFERENCE TO DIAGNOSIS.... 8
THE DIAGNOSTIC WORTH OF THE GLYCYLTRYPTOPHAN AND THE TRYPTOPHAN TESTS IN DISEASES OF THE STOMACH.... 18
THE GLYCYLTRYPTOPHAN (PEPTID) SPLITTING AGENT IN HUMAN SALIVA... 33
THE OCCURRENCE OF TRICHOMONAS HOMINIS IN GASTRIC CONTENTS, WITH A REPORT OF TWO CASES.... 51
GASTRIC ULCER WITHOUT FOOD RETENTION 66
INVOLVEMENT OF REGIONAL LYMPHATIC GLANDS IN CARCINOMA OF THE STOMACH.... 90
JEJUNOSTOMY.... 129
OPERATIVE RESULTS IN CARCINOMA OF THE GASTRO-INTESTINAL TRACT... 135
SOME OF THE DISPUTED PROBLEMS ASSOCIATED WITH SURGERY OF THE LARGE INTESTINE.... 142
THE DIAGNOSIS OF DIVERTICULITIS OF THE LARGE BOWEL.... 148
INTESTINAL DIVERTICULA: THEIR ETIOLOGY AND PATHOGENESIS.... 156
DIVERTICULA OF THE GASTRO-INTESTINAL TRACT: THEIR SURGICAL IMPORTANCE.... 188
THE RADICAL OPERATION FOR THE RELIEF OF CANCER OF THE RECTUM AND RECTOSIGMOID 203

HERNIA

THE DIAGNOSIS OF DIAPHRAGMATIC HERNIA.... 225
THE REPAIR OF HERNIA FROM THE PERITONEAL SIDE OF THE ABDOMINAL WALL.... 240
THE OCCURRENCE OF RIGHT INGUINAL HERNIA FOLLOWING APPENDECTOMY. 242

UROGENITAL ORGANS

THE CLINICAL DIAGNOSIS OF CONGENITAL ANOMALIES IN THE KIDNEY AND URETER.... 249

PAGE
THE SURGERY OF THE SINGLE AND HORSESHOE KIDNEY 265
THE RESULTS OF THE EARLY DIAGNOSIS OF URINARY TUBERCULOSIS 280
CLINICAL DATA ON MALIGNANT RENAL TUMORS 289
THE EMBRYOGENETIC RELATIONSHIPS OF TUMORS OF THE KIDNEY, SUPRARENAL, AND TESTICLE 303
THE FUNCTION OF THE URETEROVESICAL VALVE. AN EXPERIMENTAL STUDY OF THE FEASIBILITY OF URETERAL MEATOTOMY IN HUMAN BEINGS 324
A NEGLECTED PRINCIPLE IN CYSTOSCOPY 338
RESULTS IN THE TREATMENT OF TUMORS OF THE URINARY BLADDER 343
TUMORS OF THE URINARY BLADDER 353
THE FUNCTIONAL RESULTS IN PROSTATECTOMY 368
PROSTATECTOMY 376
BENIGN AND MALIGNANT OVARIAN CYSTS 393
NOTES ON CARCINOMA OF THE UTERUS 415
CESAREAN SECTION AND CESAREAN-PORRO OPERATION 422
SURGICAL TREATMENT OF PROLAPSE OF THE UTERUS AND WALLS OF THE VAGINA 429

DUCTLESS GLANDS

THE DIAGNOSIS OF DISEASES ASSOCIATED WITH ENLARGEMENT OF THE SPLEEN 441
CLINICAL OBSERVATIONS CONCERNING 27 CASES OF SPLENECTOMY 449
SURGERY OF THE SPLEEN 469
THE PATHOLOGY OF SPLENOMEGALY: A STUDY OF THE OPERATIVE AND AUTOPSY MATERIAL FROM THE MAYO CLINIC 482
FACTORS OF SAFETY IN OPERATING FOR EXOPHTHALMIC GOITER 508
GOITER 513
THE RELATIONSHIP OF THE CLINICAL AND PATHOLOGIC ASPECTS OF EXOPHTHALMIC GOITER 525
PATHOLOGIC ANATOMY OF GOITER (A MACROSCOPIC AND MICROSCOPIC STUDY OF FRESH MATERIAL FROM 2500 CASES) 536
GOITER AND ITS RELATION TO ITS STRUCTURAL AND PHYSIOLOGIC UNITS ... 546
THE SURGICAL IMPORTANCE OF THE THYMUS 556

HEAD, THORAX, SPINAL COLUMN, AND EXTREMITIES

ANALYSIS OF 13,000 CASES FOR ERRORS OF REFRACTION 629
THE RELATION OF NASAL CONDITIONS TO ANAPHYLAXIS AND ASTHMA 635
THE DIAGNOSTIC SIGNIFICANCE OF THE PARAVERTEBRAL TRIANGLE OF PERCUSSION DULNESS (GROCCO'S SIGN) 640

PAGE
SACROCOCCYGEAL SINUS (POSTANAL DERMOID) 658
REGENERATION OF THE TENDONS 665
THE OPEN TREATMENT OF FRACTURES 673
AN UNUSUAL BONE TUMOR OF THE FOOT 678

TECHNIC

MANAGEMENT OF THE OPENING IN THE TRANSVERSE MESOCOLON IN COMPLETING THE OPERATION FOR POSTERIOR GASTROJEJUNOSTOMY 683
NEPHRECTOMY WITHOUT DRAINAGE FOR TUBERCULOUS KIDNEY 686
AN APPARATUS FOR THE INJECTION AND LAVAGE OF THE PELVES OF THE KIDNEYS AND URETERS 689
AN OPERATING-ROOM MIRROR 693
A SIMPLIFIED TECHNIC FOR THE APPLICATION OF THE GLYCYLTRYPTOPHAN TEST TO GASTRIC CONTENTS 696
A METHOD FOR THE MICROSCOPIC EXAMINATION OF GASTRIC EXTRACTS AND OF FECES 699

GENERAL PAPERS

GRAFTING AND TRAUMATIC DISSEMINATION OF CARCINOMA IN THE COURSE OF OPERATIONS FOR MALIGNANT DISEASE 705
CONTRIBUTIONS OF THE NINETEENTH CENTURY TO A LIVING PATHOLOGY 711
THE MICROSCOPIC EXAMINATION OF FRESH TISSUES FOR THE DIAGNOSIS OF EARLY CANCER 721
FATAL POSTOPERATIVE EMBOLISM 727
COMPLICATIONS FOLLOWING SURGICAL OPERATIONS 738
DRAINAGE OF WOUNDS 748
NOGUCHI AND OTHER REACTIONS 752
MALARIA IN NORTHERN STATES 763
NOTE ON A PEPTID-SPLITTING AGENT IN HUMAN BLOOD-SERUM 768
GRADUATE INSTRUCTION IN MEDICINE 770
A SHORT VISIT TO SOME OF THE HOSPITALS IN GERMANY, AUSTRIA, SWITZERLAND, AND HOLLAND 780
OBSERVATIONS ON GERMAN SURGERY 791
ADDRESS, FEBRUARY 10, 1912 800
LAYING OF THE CORNER-STONE 803

INDEX OF CONTRIBUTORS 805
BIBLIOGRAPHIC INDEX 809
INDEX OF SUBJECTS 819

ALIMENTARY CANAL

UNIV. OF CALIFORNIA

DIFFUSE DILATATION OF THE ESOPHAGUS WITHOUT ANATOMIC STENOSIS (CARDIOSPASM)[*]

A REPORT OF 91 CASES

HENRY S. PLUMMER

In 1908[1] I reported 40 cases of "cardiospasm." In this series, 38 patients had diffuse dilatation of the esophagus. Since that time 56 cases of diffuse dilatation of the esophagus without anatomic stenosis have come under my observation. The purpose of this paper is to report the result of treating these cases by dilating the cardia with a hydrostatic dilator.

The following have been advanced as factors in the etiology: First, primary cardiospasm (Meltzer[2] and Mikulicz[3]); second, primary atony of the musculature of the esophagus (Rosenheim[4]); third, the simultaneous development of cardiospasm and paralysis of the circular musculature of the esophagus, brought about by degenerative changes in the vagi (Krause[5]); fourth, congenital predisposition (Fleiner,[6] Zenker,[7] and Sievers[8]); fifth, primary esophagitis (Martin[9]); sixth, kinking at the hiatus œsophagi; seventh, gross lesions of the esophagus or stomach, such as ulcer, carcinoma, etc.; eighth, congenital or acquired asthenia. That some disturbance of the nerve-muscle mechanism of the esophagus and cardia is responsible for the diffuse dilatation of the esophagus without anatomic stenosis seems to be the consensus of opinion.

Most American authors, following Mikulicz, have reported these cases under the heading "cardiospasm." The adoption of this term is premature and confusing, as the part that cardiospasm plays in the production of diffuse dilatation is by no means established, and there are many cases, probably not directly related, that have spasm at the cardiac orifice without dilatation of the esophagus.

---

[*] Read in the Section on Surgery of the American Medical Association, at the Sixty-third Annual Session, held at Atlantic City, June, 1912. Reprinted from the "Jour. Amer. Med. Assoc.," June 29, 1912, vol. lxviii, pp. 2013, 2014.

It is beyond the scope of this paper to discuss in detail the theories regarding the etiology of diffuse dilatation of the esophagus without anatomic stenosis or the etiology of cardiospasm. I wish, however, to call attention to a few points that have proved of practical interest in classifying these cases.

One hundred and thirty cases that have come under my observation have been grouped as follows:

1. Diffuse dilatation of the esophagus without anatomic stenosis, 91 cases. No gross gastric lesions were found in this group, and only 5 of the patients were of a neurotic type.

2. Severe cardiospasm without diffuse dilatation of the esophagus, 2 cases. Both patients had periodic attacks continuing from three to fourteen days, during which they were not able to swallow either liquid or solid food. I think that in these cases diffuse dilatation of the esophagus would have ultimately developed.

3. Cardiospasm without diffuse dilatation, but with gross lesions in the stomach, 12 cases. Of these, 2 patients had ulcer, 2 syphilis, 5 carcinoma, and 3 suspected, but not absolutely demonstrated, ulcer.

4. Mild cardiospasm without diffuse dilatation of the esophagus or gastric lesions, 24 cases. Almost without exception these patients were of a neurotic type, and many were distinctly hysteric.

That relatively few individuals of a neurotic type and none with gross gastric lesions were noted in the group having diffuse dilatation of the esophagus; that diffuse dilatation had not followed the cardiospasm in any of the patients with gastric lesions, and that almost constant evidence of an acquired or congenital asthenia was present in the patients with mild spasm without dilatation or gastric lesions, seem to indicate that these groups are of different origin and not very definitely related.

Ten cases which will be reported in another paper should be mentioned here. Five had some anatomic deformity at the cardia or hiatus œsophagi, and 5 a condition that is perhaps analogous to that found in congenital pyloric stenosis.

The diagnosis of diffuse dilatation of the esophagus without anatomic stenosis should rest on the demonstration of the dilatation and the absolute elimination of organic strictures. I presented the general principles of the technical methods of diagnosis[10] before this section in 1909.

Russel, in 1898,[11] was the first to report a sufficient series of cases to demonstrate the efficacy of dilating the cardia with a silk-covered rubber balloon. Russel's work did not attract attention until Sippy,[12] in 1906, reported a series of cures attained by this method. The description of the instrument and the technic which I have used since 1906 may be found in "The Journal."[1]

After eliminating the questionable cases previously referred to and the cases of cardiospasm without diffuse dilatation of the esophagus, there are 91 cases of diffuse dilatation of the esophagus without anatomic stenosis in my series. Of these, 4 patients have died, 3 cannot be traced, 73 have been completely relieved of the dysphagia, and 11 are not completely cured. Among the deaths are 2 from pneumonia, 1 from tuberculosis, 1 cause of death unknown, and 1 (Case 62) from rupture of the esophagus. Of the patients who died from tuberculosis or pneumonia, all had been free from dysphagia for a period of two or more years. The cured patients have been free from dysphagia as follows: Three between six and seven years; 12 between five and six years; 9 between four and five years; 14 between three and four years; 13 between two and three years; 12 for one year, and 10 for less than one year. Included among the cured patients are a few who, at long intervals, are conscious of the food passing the cardia.

Of the patients not completely cured, 2 came under observation over four years ago; 4 over three years ago; 1 over two years ago; 2 over one year ago; and 2 within the last year. In 5 the treatment has not been sufficiently well followed up; 2 are of comparatively recent date, and will require further treatment; 3 have had recurrences of dysphagia and regurgitation of food from the esophagus. They go, however, from periods of two to ten months without serious trouble. Two patients who were badly emaciated and regurgitated the greater part of their food still occasionally regurgitate and require water to wash down the food.

In my earlier work I determined the degree of pressure largely by the tolerance of the patient, as indicated by the evidence of pain at the moment of greatest distention. The pressure was gradually raised at successive treatments until satisfactory results were obtained. In the majority of the first 30 cases the esophagus was dilated with a pressure of 500–575 mm. of mercury; in the next 31, with a pressure of 675 mm. of mercury. In case 62 the esophagus ruptured and the patient died of general peritonitis. The manometer indicated a pressure of 720 mm. at the time the rupture occurred. In the succeeding 45 cases the esophagus was dilated with a pressure of 575–600 mm. The number of cases in which dilatation was obtained with a pressure of 575 mm. is sufficiently large to demonstrate the relative safety of using this degree of force. While I have always stopped the first treatment on the appearance of marked suffering and felt my way at succeeding treatments, I do not believe that the pain is a reliable index for judging the pressure to be used. The patient whose esophagus I ruptured did not complain of pain until the dilator was withdrawn.

In 5 patients in whom a pressure of 575 mm. failed to relieve the dysphagia, and in 3 in whom the pain prevented me from using this pressure, I resorted to dilators of gradually increasing size, sufficient pressure being used to insure each size being distended to its maximum diameter at the cardia. This method of forcible dilatation is based on the assumption that there is some latitude between the points at which relief and rupture of the esophagus will occur. This method is tedious, as the silk bag must be strongly made and of uniform diameter throughout its length, and sufficient time must elapse between treatments to allow results to be noted.

A pressure of 675 mm. of mercury has invariably given marked relief, and in a majority of cases a complete cure. It has been the routine practice to give the patients two or three treatments and allow them to go home, with instructions to return if there is any recurrence of dysphagia. In no case have I followed up the treatment at frequent intervals over a long period of time, though a number of patients have returned at intervals of two to twelve months. It is remarkable that most of the patients with extreme inanition have needed but one treatment to effect a complete cure. In 3 patients I have had opportunity to demonstrate that the dilated esophagus has returned to normal size.

REFERENCES

1. Plummer: "Jour. Amer. Med. Assoc.," August 15, 1908, pp. 549–554.
2. Meltzer: "Berlin klin. Woch.," 1888, No. 8.
3. Mikulicz: "Deut. med. Woch., 1904, vol. xxx, pp. 17, 50.
4 Rosenheim: "Berlin. klin. Woch.," 1902, No. 45.
5. Lossen: "Deut. med. Woch.," vol. xxix, Berl. Beil., p. 94.
6. Fleiner: "Münch. med. Woch.," 1900, Nos. 16 and 17.
7. Zenker and v. Ziemssen: "Cyclopedia of the Practice of Medicine," 1878.
8. Sievers: "Hospitaltid.," 1902, No. 39, Kjobenhavn.
9. Martin: "Mitt. a. d. Grenzgeb. d. Med. u. Chir.," 1901, vol. viii.
10. Plummer: "Jour. Amer. Med. Assoc.," February 25,1911, pp. 560–564; also "Trans. Sect. on Surg., Amer. Med. Assoc.," 1910, pp. 345–353.
11. Russel: "Brit. Med. Jour.," June 4, 1898.
12. Sippy: Paper read at the meeting of the American Medical Association in 1906. Not published.

NOTES ON THE DYSPEPSIAS

WITH SPECIAL REFERENCE TO DIAGNOSIS*

GEORGE B. EUSTERMAN

The types of dyspepsia chiefly considered in this discussion will be those which are recurrent or which run a chronic course—types which are usually painful and resistant to ordinary methods of relief, and which make up a large proportion of the cases examined in the Mayo Clinic.

The diagnostician may find it convenient to regard chronic dyspepsia as belonging to one of four groups. Briefly, the classification may be as follows: First, gross or surgical lesions of the stomach and duodenum—namely, chronic simple ulcer and cancer; second, reflex dyspepsias resulting from diseased conditions of the gall-bladder and appendix chiefly; third, dyspepsias dependent on or associated with constitutional diseases, such as cardiac, renal, and hepatic disease, pernicious anemia, chronic pulmonary tuberculosis, arteriosclerosis, syphilis, and diseases of the central nervous system; fourth, the so-called functional disturbances of the stomach, including gastroptosis.

The first two groups may be regarded as the surgical types, the last two, as the medical types, of dyspepsia. The large percentage of patients presenting themselves at the Mayo Clinic with chronic gastric disturbances and who have undergone an operation show no demonstrable lesion of the stomach or duodenum. The greater incidence of gall-bladder disease and appendicitis makes up for a major percentage of such cases having a dyspeptic syndrome. It is also to be remembered that chronic indigestion has an occasional source in tuberculosis or malignant states of the cecum or colon, pelvic disorders, pancreatitis, chronic constipation, migraine, disturbance or disease of the thyroid, and rarely cardiospasm, when advanced, with dilatation and food stasis. In many cases the diagnosis is often difficult, taxing all the resources of the clinician. In the surgical types the possibility of two or more lesions must be borne in mind. A surgical lesion implicating other organs on account of inflammation, perforation, or adhesions, often confuses the clinical picture so that frequently a definite diagnosis, even with the aid of skilful laboratory evidence, can be established only by an exploratory laparotomy. This is also true of a certain small percentage of recurring distressing upper or midabdominal symptoms, in which the pathology as described in the operating-room reveals a familiar lesion, but in which a definite or probable diagnosis could not be made, owing to atypical features or the lack of sufficient symptoms. On the medical side, discrimination should always be used, or the internist may occasionally fail in the recognition of a probable grave condition associated with epigastric symptoms; for example, the dyspepsia and anginoid pains of coronary sclerosis—myocardial insufficiency —or the gastric crises of tabes. On the other hand, there is always a large number of patients with a definite trend of symptoms, which, if properly elicited, should insure a fairly correct diagnosis.

---

* Read before the Macon County Medical Society, Macon, Mo., October, 1912. Reprinted from the "Journal of the Missouri State Medical Association," May, 1913.

Surgical lesions of the stomach, duodenum, gall-bladder, and appendix often present many symptoms in common in respect to disturbances of digestion owing to reflex secretory and motor disturbances. I will not, however, discuss the probable embryologic and physiologic reason for this association of symptoms or pathology. These surgical types will be considered separately as to symptom-complex, and collectively for the purpose of differential diagnosis.

1. *Duodenal Ulcer.*—Duodenal ulcer is unquestionably a more frequent surgical lesion than gastric ulcer. This rule applies in both sexes. In 1000 operative cases of benign ulcers in the duo-

denum and stomach as studied in the Mayo Clinic, duodenal ulcer was present in 572 cases and gastric ulcer in 428 cases. "This is not a fair relative percentage, however, because the earlier cases in which an ulcer was found in the vicinity of the pylorus were classified as gastric, and in all probability many of them were duodenal in origin."

"From June 1, 1906, to January 17, 1911, 621 cases of gastric and duodenal ulcer were operated on, of which 201 (32.5 per cent.) were gastric, 401 (64.5 per cent.) duodenal, and 19 (3 per cent.) were shown to have an ulcer of each viscus. That at least 2 out of 3 cases of ulcer will be found to have their origin in the duodenum, rather than the stomach, is a conservative estimate."

"In the diagnosis of duodenal ulcer four points seem to stand out prominently in the large number of cases: (*a*) The periodicity of attacks; (*b*) the number of years (the average is 12½) through which these attacks and intermissions or remissions have run before surgical relief has been advised, or perhaps accepted; (*c*) the characteristics of pain, its great diagnostic significance, and its place in the differential diagnosis; (*d*) the ready control of all symptoms during the period of attack by the measures that control pain, *i.e.*, food, alkalis, irrigation, and vomiting." This is the type of chronic painful dyspepsia, the pain coming on from two to four hours after meals, accompanied, as a rule, by gas, distress, belching, and sour hypersecretion. The next meal usually relieves the pain. Pain may awaken the patient at a regular time each night during an attack. The appetite may remain unimpaired. There may be eructation of food, rarely vomit, in early stages, unless induced. One-third of the cases give a history of hematemesis or melena, or both. The course is usually progressive, and later attacks are associated with marked constipation and loss of weight.

The clinical picture is fairly clear in the majority of these cases. The complications are: (*a*) Pyloric obstruction with atony and dilatation; (*b*) perforation; (*c*) hemorrhage; and (*d*) adhesions to neighboring organs. The following case report is illustrative of the characteristics of this disease:

Case 72731.—J. F., male, aged forty-three. Examination August 27, 1912. Family and personal history negative. Denies venereal disease. No bad habits, although fast and irregular eater. Had measles and scarlet fever in childhood, the latter followed by "dropsy." Present symptoms: Epigastric pain and sour dyspepsia. For past twenty years has had an attack about twice a year (usually spring and fall), each one lasting six weeks or longer. Progressively worse, especially in past four or five years, on account of increased pain. Last seizure began two weeks ago, and is characteristic of previous ones: A "drawing" midepigastric pain, which comes on about two hours after each meal, and continues up to next meal-time unless relieved in the interval by food, soda, or brandy. Also awakens at night, between 12 and 1 A. M., with the pain. This is usually relieved by soda, milk, and crackers or external application of heat. During height of pain, sour, watery, burning eructation, belching, and feeling of distention. Rarely any radiation of pain. Tender to pressure. Appetite good; in fact, abnormal. Loss of weight during an attack. During intervals, free from pain and dyspepsia. Bowels fairly regular until recently. One year ago first and only hemorrhage; this was preceded by severe epigastric pain just before a noon meal; drank a cup of cold water to get relief, when he vomited coffee-ground material. The next day passed a tarry stool. No shock. Usual weight, 168 to 175 pounds; now, 161 pounds. No urinary nor pulmonary symptoms.

Physical examination: Patient fairly well nourished and good color. Head, neck, and chest objectively negative. Abdomen moderately scaphoid, resistant, and tender midepigastrium and tight upper quadrant. No peristaltic unrest. Percussion outline stomach fairly normal. Reflexes all present and normal. Moderate tenderness, McBurney area.

Urinalysis: 650 c.c. (eighteen hours); specific gravity, 1020. Acid, trace albumin. Few hyaline casts. Maximum arterial pressure, 145 mm.

Gastric analysis: Filtrate, 160 c.c.; very sour; food-bits; total acidity, 100; free HCl, 100; trace altered blood. Examination of stool (tincture of guaiac test) positive.

Diagnosis: Duodenal ulcer; chronic appendicitis.

Laparotomy September 2, 1912 (W. J. Mayo): "Large, thick duodenal ulcer, involving the anterior wall an inch or more in extent. Appendix showed recent peritonitis and contained fecal stones." Gastro-enterostomy; appendectomy.

2. Gastric Ulcer.—A differential diagnosis between gastric and duodenal ulcer is often difficult and sometimes impossible. The majority of gastric ulcers are situated in the *pars pylorica*, and closely simulate duodenal ulcer. That which has been said with reference to duodenal ulcer holds equally good for all ulcers situated in the pyloric end of the stomach. If the ulcer be in the lesser curvature, the pain and the tender points may be in the region of the left costal margin. Pain and tenderness accompanying duodenal ulcer are usually to the right and above the navel, or are midepigastric. The nearer the ulcer approaches the cardia, the earlier does pain come on after taking food. Test-meals show the acidity relatively higher in duodenal ulcer. If bleeding occurs, ulcer situated in the stomach causes hematemesis largely. Although bleeding from duodenal ulcer occurs mainly by the bowel, hemorrhage from the mouth is relatively frequent. Three to 4 per cent. of all duodenal ulcers extend to and involve the pylorus, a condition which often explains a double hemorrhage. Fluoroscopy in doubtful cases is often helpful in locating the site of the lesion. Radiographic plate of the stomach following ordinary administration of bismuth is invaluable in diagnosis of hour-glass contractions.

3. Gall-bladder.—Chronic gall-bladder disease is in many cases accompanied by a dyspeptic syndrome closely simulating the symptoms in chronic ulcer of the stomach or duodenum. This is the most frequent source of error in the diagnosis of painful upper abdominal lesions. The typical hepatic colic, with sudden onset of pain in the epigastrium, diaphragmatic bursting feeling, pain radiating into the back, sudden cessation, with or without jaundice supervening, should not be difficult to recognize. Yet a duodenal ulcer having an early tendency to perforate may have almost similar symptoms. On the other hand, the chronically diseased gall-bladder, with impacted stone, probable ulceration, and adhesion, in which no jaundice appears, and the gastric symptoms, such as gas, vomiting, burning distress, sour eructation, impaired appetite, and dilatation, predominate, in which the pain is moderate and follows food, will often be diagnosticated as ulcer.

4. *Appendiceal Dyspepsia.*—Appendiceal disease of the acute type should not offer great diagnostic difficulty. Often a vague dyspepsia may precede for some time an acute localizing seizure. In a certain percentage of chronic recurrent cases we have an associated dyspepsia, often simulating gastric disease. This is in all probability due to reflex secretory and motor disturbances in the stomach. In this type there are distinct prolonged attacks. Pain is not referred to McBurney's point, and often no appendiceal tenderness can be elicited. There may be no symptoms that accompany the usual attack of appendicitis except those directly referred to the stomach. The pain may be directly reflex, may be due to the pyloric spasm or to a gastritis, owing to chronic hypersecretion. At times, however, during the course of the disease, McBurney tenderness or a history of subjective pain in the right iliac fossa may be elicited. As a rule, there is not the regularity of onset of pain after food—the periodicity of attack—which characterizes gastric ulcer. In appendiceal disease food often causes immediate distress; rarely relieves, unless hyperacidity is present. A continuous pain, or rather a continuous distress, which is epigastric or indefinitely abdominal, is often present. Nausea, distress, flatulence, and a feeling of distention are symptoms far more common in association with chronic appendix than with chronic peptic ulcer or disease of the gall-bladder.

5. *Cancer of the Stomach.*—Cancer of the stomach, another frequent surgical condition, will be mentioned but briefly. This disease often follows upon latent or active ulcer of the stomach. In a recent study of several hundred cases which were resected in the Mayo Clinic, 60 per cent. gave a history of previous ulcer. This was corroborated by pathologic evidence, in which a series (189 cases) showed microscopic proof of preëxisting ulceration in 67 per cent. Cancer should always be excluded in a middle-aged or elderly patient who, having had no previous dyspepsia, now complains of dyspepsia, with or without pain and distress, perhaps vague at first, and associated with loss of weight and strength. In proved or strongly suspicious cases of carcinoma of the stomach

or any other part of the anatomy early surgery offers the only hope of cure or amelioration.

6. *Other Types of Diseases Which May be Associated With Dyspepsia.*—(*a*) When *syphilis* attacks the stomach or liver, it may clearly simulate ulcer of the stomach or gall-stones, and when quite advanced, the pain, cachexia, and vomiting may lead to a strong suspicion of cancer. The vomiting of the gastric crisis of tabes is misleading; however, the attacks are peculiarly sudden, the vomiting is irregular, straining, and prolonged, often following the introduction of food, but occurs if total abstinence is practised. Perhaps little pain, not often sour stomach, no hunger pain, no food relief, or other characteristics are present. The attacks cease as abruptly as they begin, leaving no signs of trouble. In addition, there may be a history of specific infection, or the Wassermann reaction may be positive. Patients may complain of lightning pains, ataxia, bladder troubles, or other symptoms suggesting tabes. Examination of the eye and patellar reflexes is most important. Specific treatment often assists in clearing up the diagnosis. It should be remembered that syphilitic ulcers of the stomach are a frequent factor in the production of an hour-glass deformity of that organ.

(*b*) Many patients with early or chronic *pulmonary tuberculosis* present themselves with a gastric complaint only, fearing ulcer or cancer. Anorexia, distress after eating, often pain, vomiting, and cachexia, are present; hydrochloric acid is absent. Tuberculosis of the intestines often gives dyspeptic symptoms. Careful examination of the chest may reveal a focus or area of involvement of the lung; an irregular fever, cough, bacilli, or other tuberculous foci may be determined.

(*c*) *Bright's disease*, often confused with gastric complications, loss of appetite, emaciation, anemia, dislike for food, vomiting, food distress, and gastric analyses, often closely follows the ulcer or cancer type of stomach trouble. Routine examination of a complete twenty-four-hour specimen of urine should be made. The total amount, specific gravity, the character of the casts, are most important. A history of increased frequency or suppression;

the previous history of infection; together with the condition of the heart, blood-vessels, retinas, and arterial pressure, will clear up the diagnosis.

(*d*) *Pernicious anemia* is often most difficult to differentiate from ulcer, and especially cancer. Unless the complete blood analysis is positive, one is often at a loss in deciding. Gastric analysis suggests cancer. There may be lack of appetite in both, distress after food, nausea, gas, and blood, also constipation and loss in weight. In cancer and anemia there may be pain, shortness of breath, and palpitation on exertion, which conditions are more marked in anemia than in cancer. We do not usually find the pain and vomiting of cancer. There is less emaciation in anemia; the skin is more apt to be a lemon color than colorless; there is an "oilier" feel present, and a slight general edema is usually found. The skin of cancer is dry, and often of a grayish hue. The stomach analysis in anemia is misleading. Tumor is never present in this disease. The characteristic wave of improvement and relapse may mark the clinical course. A differential diagnosis may be established if definite improvement follows the administration of iron and arsenic, together with rest, enemas, proper feeding, etc.

The Functional Dyspepsias.—This group forms a very considerable percentage of the cases observed in the Mayo Clinic. They are viewed from the standpoint of probable non-surgical cases of dyspepsia. Grossly, they may be separated from the surgical types of—(*a*) Usually no definite pain association; (*b*) very little or no nutritional disturbance, often steady gain in weight in spite of prolonged or marked dyspeptic syndrome; (*c*) complaint more often daily or constant, not periodic, which is usually a characteristic of the uncomplicated surgical type; (*d*) a large percentage have a nervous, functional basis, and thus are accompanied by or follow nervous or neurotic manifestations. The absence of sufficient distress or pain to awaken the patient at night is often noted in these cases.

Fenwick's classification of these cases, which is appended, is comprehensive and practical.

1. Disorders of secretion.
    - (*a*) Hyperacidity or an increase of HCl.
    - (*b*) Hypersecretion, or continuous gastric secretion.
    - (*c*) Subacidity (achylia), or diminished gastric secretion.
2. Disorders of mobility.
    - Myasthenia gastrica (atonic dyspepsia), or enfeeblement of the muscular coat of the stomach.
3. Disorders of the nervous mechanism.
    - (*a*) Hyperesthesia of the stomach.
    - (*b*) Neurasthenia gastrica (nervous dyspepsia).
    - (*c*) Nervous eructation and regurgitation.
4. Dyspepsia due to inflammation of the stomach.
    - (*a*) Acute gastritis.
    - (*b*) Chronic gastritis.
    - (*c*) Atrophic gastritis.
5. Dyspepsia dependent upon displacements of the stomach.
    - Gastroptosis.

These cases often present great problems to the diagnostician. They may possess characteristics of both motor and secretory disturbances. A functional dyspepsia may complicate a surgical lesion. Cases with early, mild, indefinite gastric disturbances, dependent on gall-bladder or appendiceal disease, are often included in this group, until subsequent localizing symptoms explain the probable etiology. Cases of functional hyperacidity may simulate ulcer. Test-meal analyses of hyperacid cases and chronic catarrh are similar to those found in gastric or duodenal ulcer and cancer respectively. A mixed neurosis, affecting both sensation and mobility, and accompanied by symptoms of general neurasthenia, constitutes the obscure and complex disorder known as neurasthenia gastrica, or nervous dyspepsia. Alterations in the position of the stomach, whether congenital or acquired, oppose a mechanical obstacle to the propulsion of food into the duodenum, and by causing secondary perversions of the other gastric functions, may give rise to a form of dyspepsia which can be distinguished from gastric neurasthenia only by careful examination.

Conclusion

The essential factors in the proper diagnosis of gastric and allied conditions which cause dyspepsia are:

(1) Careful history-taking.

(2) Routine, thorough physical examination.

(3) A routine test-meal examination.

(4) If necessary, a skiagraph series or fluoroscopic study of the gastroduodenal area.

(5) A correct interpretation of all the data at hand.

(6) The general attitude of the patient, his general appearance, etc., should be observed. The careful physician should inquire into the daily habits, social environment, manner of eating, nature of food, condition of teeth, etc. He should correct the diet, urge proper mastication, and institute natural, therapeutic, or surgical measures, as the case may be.

REFERENCES

1. "Collected Papers by the Staff of the Mayo Clinic, St. Mary's Hospital," 1910 and 1911.
2. Fenwick: "Dyspepsia: Varieties and Treatment."

THE DIAGNOSTIC WORTH OF THE GLYCYL-TRYPTOPHAN AND THE TRYPTOPHAN TESTS IN DISEASES OF THE STOMACH *

A REPORT OF 1175 CASES STUDIED BY A UNIFORM METHOD

FRANK SMITHIES

The surgeon and the pathologist have shown that, when cancer of the stomach is diagnosed early, that affection is as amenable to treatment as is cancer in other parts of the gastro-intestinal tract. At present it would seem that early diagnosis rests largely on microscopic examination of sections of extirpated tissue. Inasmuch as prognosis is directly dependent on the process at diagnosis, it would appear desirable to elaborate certain diagnostic procedures that might anticipate findings at laparotomy.

Recently the physiologic chemist has undertaken the investigation of biologic problems bearing on clinical medicine. Various workers, notably Muller,[1] Fischer,[2] and Abderhalden,[3] have reported that malignant neoplasms contain certain peptidolytic enzymes. This discovery appeared to have clinical value when Neubauer and Fischer[4] announced that simple peptids, particularly the dipeptid, glycyltryptophan, were hydrolyzed by cancerous ferments. In the case of glycyltryptophan, the amino-acid, tryptophan, which is liberated by this cleavage, can be recognized readily in acid solution by the rose-pink color occurring on the addition of bromin. This reaction forms the basis of the "glycyltryptophan test" for cancer of the stomach, advanced by Neubauer and Fischer.

---

* Read before the American Gastro-enterologic Society, Atlantic City, June 3–4, 1912. Reprinted from the "Archives of Internal Medicine," October, 1912, vol. x, pp. 357–368.

Clinicians generally have disagreed widely on the actual value of the test. The reaction's sponsors, together with Lyle and Kober[5] and Weinstein,[6] early reported enthusiastically on the procedure. Later observers, especially Warfield,[7] Oppenheim,[8] Kohlenberger,[9] and, most recently, Sanford and Rosenbloom,[10] declare that the test is of dubious value. They admit that while certain cases of cancer of the stomach undoubtedly give the reaction, many non-malignant gastric disturbances give similar tests. Factors claimed to influence the reliability of the reaction are swallowed saliva, bacteria, bile, or blood in the gastric extracts, low or absent free hydrochloric acid, and regurgitated duodenal contents.

In October, 1911, Weinstein[11] announced that he had improved on the Neubauer and Fischer test. He stated that in extracts from cases of carcinoma ventriculi there exist free amino-acids, notably tryptophan, and that the latter can be tested for directly with bromin. This procedure appeared to render unnecessary the addition of glycyltryptophan to such gastric contents, with search for its cleavage products subsequently. This so-called "tryptophan test" was claimed as a reaction pathognomonic of cancer of the stomach. Weinstein did not, however, go so far as to state just how early in the progress of the disease this test could be regarded as pathognomonic. Certainly, in the clinical cases which he briefly quoted, when the tryptophan test was positive, other evidences of cancer were not lacking. Recently Hall and Williamson[12] and Sanford and Rosenbloom[10] have recorded observations which appear to indicate that Weinstein's test has even less value than, in their experience, had the glycyltryptophan test.

The great difference of opinion regarding the practical worth of the two tests mentioned led us to make the observations herewith submitted.

AUTHOR'S STUDY

From October 1, 1911, to May 15, 1912, the Ewald test-breakfast was administered to 1626 different individuals at the Mayo Clinic. On the gastric extracts from more than 1400 of these patients glycyltryptophan and tryptophan tests were made. On 1175 different individuals the gastric extracts were tested according to the modification of the glycyltryptophan and the tryptophan tests recently suggested by me.* This modification appears to have the advantages of requiring less of the test ingredients than the Neubauer and Fischer method, of being a controlled procedure, and one in which the end-reaction may be easily determined. It is the purpose of this communication to report our experience with the cases tested by this uniform method.

---

* The test is set up as follows:

1. Test-tubes of 10 c.c. capacity are employed. These should be carefully cleaned with boiling water and dried inside. They are numerically marked for identification with a wax pencil. Into each test-tube is carefully measured, by means of a sterile graduated pipet, 0.5 c.c. of the glycyltryptophan solution. Five c.c. of the recently secured filtered gastric extract is then measured by a clean graduated pipet and poured into the correspondingly numbered test-tubes, to which glycyltryptophan solution has been already added. Two control tubes are used. In one is placed 0.5 c.c. of glycyltryptophan solution and 5 c.c. of normal salt solution, and into the other is placed 5 c.c. of normal salt solution without added glycyltryptophan solution. In the entire series each tube next receives 0.5 c.c. of toluol (toluene, Merck). The contents of the tubes are then mixed by inverting several times. The tubes are next placed in a water-bath (an incubator may be used) at 37° C. for twenty-four hours.

2. At the expiration of the incubation period the test-tubes are removed from the water-bath. Clean test-tubes of 10 c.c. capacity, and numbered to correspond with the gastric extracts tested, as well as the controls, are set in racks. Into each of these tubes is measured, by means of a graduated pipet, 2 c.c. of the glycyltryptophan-gastric-extract mixture lying below the toluol in the recently incubated tubes. To each tube are then added three drops of a 3 per cent. glacial acetic acid in distilled water solution. The tubes are well shaken. Bromin vapor is allowed to flow into each tube until it appears amber yellow above the contained fluid. The tubes are again shaken. Examination by daylight (preferred) or by white, artificial light is now made for evidences of the characteristic rose-pink reaction between the amino-acid (tryptophan) and the bromin.

Tryptophan Test.—As suggested by Weinstein, this is made, as routine, on the fresh gastric extracts, inasmuch as, occasionally, swallowed saliva, amino-acids, regurgitated duodenal contents, and the like may give the bromin vapor reaction, before incubation or without the addition of a dipeptid, such as a glycyltryptophan. Five c.c. of each fresh, filtered gastric extract are poured into test-tubes of 10 c.c. capacity, acidulated with the 3 per cent. acetic acid solution and treated with bromin vapor as above. If no characteristic rose-pink color results, the tubes are incubated with the corresponding specimens that have been mixed with glycyltryptophan solution. For accurate work it has seemed best to us to cover these "tryptophan test" contents with a layer of toluol. At the end of twelve, twenty-four, and forty-eight hours note is made of changes in color, and these results are compared with those obtained with the preparations in the first series.—"*Jour. Amer. Med Assoc.*," 1912, vol. lvii, p. 1008.

Certain precautions taken in the manipulation of the reaction might be mentioned briefly. All glassware was boiled in distilled water and dried before using. The solution of glycyltryptophan employed was obtained, in bulk and unopened, direct from the makers. To guard against its tendency to crystallize out, in cold solution, the preparation was kept in a water-bath at 37° C. until used. All gastric extracts were carefully filtered before testing, and the tests were set up within two hours, at the outside, from the time the contents were taken from the patients. In testing for tryptophan, before or after incubation, bromin vapor was preferred over bromin water. It is more readily controlled quantitatively, and permits of better color determination. All end-reactions were read by daylight.

TYPICAL REACTIONS

When bromin vapor is used for the detection of amino-acid (tryptophan), its presence is indicated, even in small amounts, by lilac-violet to rose-pink shades. The color is usually a lively one, and appears quickly. Admixtures of much blood and bile produce, respectively, dirty, brownish-yellow, and muddy-green to drab. In such, gradations in shade are impossible. High organic acidity often gives rich purple or magenta hues. When the color change is opalescent, with bluish or delicate lilac cast, the results may be classed safely as negative.

RESULTS

The gross results of our observations are as follows: Of 1175 gastric extracts from individuals with gastric symptoms, clinically, 110, or 9.36 per cent., were glycyltryptophan positive. In the same cases, 24, or 2.04 per cent., were tryptophan positive, either before or after incubation. Tables 1 and 2 show, respectively, the number of positives with each test associated with different diseases. Tables 3 and 4 respectively consider the clinical and laboratory data.

TABLE 1.—SUMMARY OF CASES GIVING POSITIVE GLYCYLTRYPTOPHAN TEST

Diagnosis	Number of Cases	Diagnosis	Number of Cases
Carcinoma ventriculi	31	Achylia gastrica	6
Ulcus ventriculi	9	Appendicitis	8
Carcinoma of the liver	3	Primary anemia	3
Ulcer of duodenum	3	Syphilis—stomach	1
Non-malignant pyloric obstruction	1	Various (gastritis, gastric neurosis, chronic diarrhea, epilepsy)	10
Cholecystitis	11		
Gall-stones	6		
Hypochlorhydria	7	Total	110
Achlorhydria	11		

TABLE 2.—SUMMARY OF CASES GIVING POSITIVE TRYPTOPHAN TEST

Diagnosis	Number of Cases	Diagnosis	Number of Cases
Carcinoma ventriculi	7	Appendiceal lesions	1
Ulcus ventriculi	3	Various (neuroses, achlorhydria, arteriosclerosis)	6
Ulcer of duodenum	3		
Carcinoma of the liver	1		
Gall-stones	3	Total	24

It will be noted that one of the valuable features of the tables is the fact that the majority of the cases exhibiting positive reactions were treated surgically; hence the conclusions derived from consideration of the figures returned have a fairly definite pathologic basis.

TABLE 3.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE GLYCYLTRYPTOPHAN TEST

No.	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
61563	Gall-bladder infection	46	36	+	0	0	+
9532	Anemia (postmortem)	0	0	+	0	0	+
61743	Duodenal ulcer—operation	86	80	0	++	0	+
61000	Cholecystitis	46	40	0	0	0	+
61795	Gastritis, chronic	14	6	+	0	0	+
61857	Carcinoma of stomach—operation	0	0	++	0	0	++
61802	Gastritis; chronic appendicitis	4	0	+	+	?	+
38406	Gall-bladder infection	6	0	0	0	0	++
53228	Gastric neurosis	18	18	+	0	0	++
61852	Carcinoma of stomach	4	0	+	0	0	++
61910	Carcinoma of stomach—operation	0	0	++	0	++	+

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

TABLE 3.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE GLYCYLTRYPTOPHAN TEST—(*Continued*)

No.	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
61812	Epilepsy	10	10	+	+	0	++
61940	Gastritis, chronic	24	24	0	0	0	+
61862	Gastric neurosis	40	30	0	+++	0	+
61974	Gastritis, alcoholic	0	0	+	+	+	+++
62100	Carcinoma of stomach—operation	20	0	+	0	+	+
62171	Carcinoma of stomach—operation	48	0	+	0	++	+
62086	Gastritis, chronic	10	0	0	++	0	+
62089	Gastric ulcer	40	40	0	+	0	+
62219	Carcinoma of stomach—operation	24	12	+	0	0	+
62154	Carcinoma of stomach—operation	8	0	0	+	0	++
62233	Carcinoma of liver—exploratory	24	24	+	+	0	++
62260	Pyloric obstruction, non-malignant	40	32	++	+	0	+
62399	Carcinoma of stomach—operation	0	0	+	0	0	+
53032	Duodenal ulcer—operation	50	50	Tr.	+	0	+
62562	Carcinoma of gall-bladder—operation	6	0	+	+	0	+
62665	Gastric ulcer	28	28	Tr.	+	0	++
37124	Carcinoma of stomach, recurrent	8	0	0	+	0	+
61072	Gall-stones—operation	56	40	0	Tr.	0	+
62876	Cholecystitis	10	0	Tr.	++	0	+++
62912	Chronic appendicitis—operation	22	18	Tr.	+	0	+
62971	Chronic appendicitis—operation	22	0	0	+	0	+
62977	Ulcer of stomach	48	40	0	0	0	+
63026	Chronic appendicitis	32	32	+	+	0	+
63051	Negative, stomach, appendix	36	32	0	+	0	+
63093	Chronic diarrhea, stomach negative	4	0	0	0	0	+
63129	Gastric ulcer and gall-bladder operation	32	30	+	0	0	0
63130	Chronic appendicitis—operation	0	0	0	0	0	+
62699	Cholangitis	0	0	Tr.	0	0	+
63030	Carcinoma of stomach	8	0	0	0	0	+
63241	Carcinoma of stomach—operation	56	18	+	0	0	+
63292	Gastric ulcer	46	46	+	+	0	+
63197	Multiple sclerosis	20	6	0	+	0	+
63335	Duodenal ulcer; cholecystitis	48	40	0	+	0	+
52034	Recurrent carcinoma of stomach	10	0	+	+	0	+
62876	Syphilis of stomach	0	0	0	0	0	+
63506	Gastritis	38	22	0	+	0	+
63547	Resection of stomach (carcinoma)	0	0	+	0	?	+
63562	Arteriosclerosis	0	0	0	0	0	+
63600	Appendicitis—negative	44	40	0	+	0	+
63616	Appendix and gall-bladder operation	12	0	0	+	0	+
63653	Ulcer of stomach—operation	32	28	Tr.	+	0	+
63636	Gall-stones—operation	22	0	0	0	0	+

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

TABLE 3.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE GLYCYLTRYPTOPHAN TEST—(*Continued*)

No.	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
63778	Carcinoma of stomach	14	0	+	+	+	+
36634	Ulcer of stomach	40	30	+	0	0	+
63883	Gall-stones—operation	6	6	0	0	0	+
64057	Hypochlorhydria	8	0	+	++	0	+
64039	Achlorhydria	0	0	0	0	0	+
61915	Hypochlorhydria	4	4	0	0	0	+
64270	Ulcer of stomach—operation	50	46	+	0	0	+
64330	Carcinoma of stomach	14	0	+	0	+	+
64360	Neurosis	54	50	0	+	0	+
64482	Carcinoma of stomach, resection	8	0	+	0	0	+
64455	Hypochlorhydria	4	0	+	0	0	+
64281	Achylia gastrica	0	0	+	0	0	+
34078	Neuroses	42	40	0	0	0	+
64877	Cholecystitis	4	0	0	0	0	+
65179	Appendicitis	36	26	0	Tr.	0	+
65229	Carcinoma of stomach and liver	0	0	+	0	0	+
65293	Achlorhydria	8	0	0	+	0	+
65337	Cholecystitis, appendix	16	0	0	Tr.	0	+
37889	Appendicitis—operation	12	12	Tr.	0	0	+
65693	Gall-stones and appendix—operation	38	14	24	+	0	+
22528	Duodenal ulcer—operation	8	0	0	0	0	+
65703	Degenerated gastric ulcer	8	0	0	0	0	+
65835	General carcinoma, primary in the stomach	0	0	0	0	0	+
65901	Carcinoma of stomach	6	0	+	0	0	+
5231	Achlorhydria	8	0	0	+	0	+
65953	Achlorhydria	12	0	0	+	0	+
66017	Carcinoma of stomach	30	0	+	0	0	+
66108	Gall-stones—operation	8	0	0	+	0	+
66225	Pernicious anemia	40	0	+	0	0	+
64942	Secondary anemia	10	0	0	0	0	+
66314	Cholecystitis	30	30	0	+	0	+
66333	Gall-stones—operation	10	0	+	0	0	+
66409	Achlorhydria	20	0	+	0	0	+
66462	Gastric ulcer	26	26	+	0	0	+
56586	Cancer of stomach, recurrent	48	48	0	0	0	+
66466	Achlorhydria	48	0	0	0	0	+
63547	Cancer of stomach—resection	12	0	Tr.	0	0	+
66511	Achlorhydria	4	0	0	0	0	+
66583	Cholecystitis	50	50	0	0	0	+
66644	Carcinoma of stomach	12	0	0	0	0	+
66787	Achlorhydria	20	0	Tr.	0	0	+
66904	Achlorhydria	34	0	Tr.	0	0	+
66855	Carcinoma of stomach—operation	26	26	+	0	0	+
66864	Hypochlorhydria	12	12	+	0	0	+
67000	Degenerated gastric ulcer	26	26	+	0	0	+

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

Table 3.—Clinical and Laboratory Data of the Cases Returning Positive Glycyltryptophan Test—(*Continued*)

No.	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
45833	Hypochlorhydria	8	8	+	0	0	+
67110	Cancer of stomach	20	0	+	0	+	+
67112	Gastric neurosis	38	24	0	0	0	+
67077	Carcinoma of liver and spleen	80	80	0	0	0	+
67206	Carcinoma of stomach	14	0	0	+	0	+
67295	Hypochlorhydria	18	8	Tr.	+	0	+
67368	Carcinoma of stomach	50	50	+	0	0	+
67690	Pernicious anemia	4	0	0	+	0	+
67928	Carcinoma of stomach, pernicious anemia (?)	14	0	+	0	0	+
67562	Gall-stone—operation	12	0	0	0	0	+
67537	Exploratory, for cancer of stomach	20	0	0	0	0	+
67644	Achlorhydria	4	0	0	0	0	+

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

Cancer.—The total number of proved cases of cancer of the stomach, primary or secondary, in this series is 87. Of this number, 31, or 35.6 per cent., gave positive glycyltryptophan tests, while 7, or 8.04 per cent., were tryptophan positive. Of the 31 cases of cancer in which the glycyltryptophan test was positive, the tryptophan test was positive but 4 times. In 3 cases in which the tryptophan test was positive the glycyltryptophan test was negative.

Of 9 gastric ulcers with fair evidence of carcinomatous degeneration (of the type described by MacCarty[13]), 2, or 22.2 per cent., gave the glycyltryptophan reaction. In these same cases there was no positive tryptophan test. If we combine the returns from these cases with those from the specimens of advanced carcinoma, we note that the glycyltryptophan test is positive in 35.4 per cent., and the tryptophan in 7.28 per cent., or the glycyltryptophan test is positive approximately 5 times as frequently as is the tryptophan test.

Gastric Ulcer.—In none of 35 operated gastric ulcers (microscopically carcinoma-free) was the glycyltryptophan test positive. The tryptophan reaction was obtained once.

TABLE 4.—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE TRYPTOPHAN TEST

OFFICE NO.	DIAGNOSIS	TOTAL ACIDITY	FREE HCl	BLOOD	BILE	LACTIC ACID	DEGREE OF REACTION*
61508	Stomach negative	36	36	0	+	0	+
61496	Duodenal ulcer—operation	56	38	0	0	0	+
61567	Gastric ulcer	42	20	0	+	0	+
61552	Carcinoma of stomach, inoperable	38	18	+	0	+	++
62233	Carcinoma of liver and gall-bladder	24	24	+	+	0	++
62784	Gastric ulcer, clinical	12	12	+	0	0	+
62876	Achlorhydria and gall-bladder disease	10	0	+	++	0	+
62865	Appendix, chronic	24	18	Tr.	+	0	+
63051	Gastric neurosis	36	32	0	+	0	+
63230	Carcinoma of stomach (mass)	8	0	0	0	0	+
63241	Gastric carcinoma, resection	58	18	+	0	0	+
63221	Gall-stone, empyema of gall-bladder	20	20	0	Tr.	0	+
63414	Duodenal ulcer operation	80	80	0	+	0	+
63408	Carcinoma of stomach—operation	66	60	0	0	0	+
63653	Gastric ulcer, clinical	32	28	Tr.	0	0	+
63354	Tabes—crises	4	0	+	0	0	+
63563	Arteriosclerosis, general	0	0	0	0	0	+
63536	Gall-stone—operation	22	0	0	0	0	+
64394	Duodenal ulcer—operation	66	60	0	0	0	+
64294	Carcinoma of stomach—operation	14	4	+	0	+	+
65693	Gall-stones and appendicitis—operation	38	14	+	0	0	++
5231	Gastric ulcer, degenerative, post-operative	8	0	0	+	0	++
56586	Carcinoma of stomach, recurrent	48	0	0	0	0	+
67112	Gastric neurosis	38	24	0	+	0	++

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.

Thirty-nine cases were clinically diagnosed as gastric ulcer. Three of these (7.4 per cent.) were glycyltryptophan-positive, and 2 (5.2 per cent.) were tryptophan-positive.

Duodenal Ulcer.—Operations were performed on 78 patients with duodenal ulcers. Of this number, 3 (2.6 per cent.) gave glycyltryptophan and tryptophan tests. They were not identical cases, and the reactions were not always associated with low acidity.

Fifty-seven individuals had duodenal ulcer clinically. One (1.7 per cent.) was glycyltryptophan-positive. None gave the tryptophan test.

Other Gastric Conditions.—It has been advanced by Weinstein, Warfield, and Sanford and Rosenbloom that positive glycyltryptophan reactions are usually obtained in gastric extracts exhibiting achylia or low hydrochloric acid. These reactions are claimed to result from the presence of a peptid-splitting enzyme (Warfield) existing in saliva. Gies[14] thinks that mouth-bacteria may be capable of splitting simple peptids under these conditions. In order to determine the results in our cases from the viewpoint of acidity, we have compiled Tables 5 and 6. It will be seen that about 60 per cent. of the positive glycyltryptophan tests were obtained from extracts showing no free hydrochloric acid, while in an additional 13.6 per cent. the free hydrochloric acid was low. In other words, nearly three-fourths of the positives occurred in gastric extracts showing diminished acidity. Table 5 also brings out the interesting fact that approximately 80 per cent. of the glycyltryptophan reactions were returned by contents in which the total acidity was low.

TABLE 5.—THE RELATION OF GLYCYLTRYPTOPHAN TEST TO ACIDITY

Group	No. of Positives	No. of Negatives	Group	No. of Positives	No. of Negatives
Extracts having no acidity..........	14	20	Extracts having decreased T. A......	88	515
Extracts having no free HCl.........	52	31	Extracts having normal T. A.........	17	213
Extracts having diminished HCl	15	214	Extracts having increased T. A......	5	337
Extracts having normal HCl.........	22	369	Totals.........	110	1,065
Extracts having increased HCl......	7	431	Extracts having lactic acid..........	11	33
Totals.........	110	1,065			

The support which these figures apparently give to Warfield's saliva ferment-action on peptids is qualified when one considers the negative glycyltryptophan tests in Table 5. Fifty-one of these extracts showed no free hydrochloric acid. In 214 extracts the free hydrochloric content was diminished. The combination of these results demonstrates that about one-fourth (24.8 per cent.) of the negatives were associated with low free hydrochloric acid. It could scarcely be maintained that all these extracts were saliva-free. Table 3 shows that some of the extracts were from cancerous patients. Approximately one-half (48.3 per cent.) of the negative glycyltryptophan tests were on extracts with diminished total acidity.

TABLE 6.—THE RELATION OF TRYPTOPHAN TEST TO ACIDITY

Group	No. of Positives	No. of Negatives	Group	No. of Positives	No. of Negatives
Extracts having no acidity	1	33	Extracts having decreased T. A.	17	586
Extracts having no free HCl	6	77	Extracts having normal T. A.	2	228
Extracts having diminished HCl	10	219	Extracts having increased T. A.	5	337
Extracts having normal HCl	4	387	Totals	24	1,151
Extracts having increased HCl	3	435	Extracts having lactic acid	2	42
Totals	24	1,151			

A consideration of the relation of the tryptophan test to acidity is of interest. Of the positives, 7, or 28.9 per cent., of the contents contained no free hydrochloric acid. In 17 (75 per cent.) of the positives the free hydrochloric acid was diminished or absent. This combined figure is practically identical with that returned by the glycyltryptophan positives, although the percentage of extracts containing no free acid is much lower. In the tryptophan positives it will be seen that 75 per cent. showed diminished total acidity, as against 80 per cent. in the case of glycyltryptophan positives.

Studying the negative tryptophan reactions, we note that in 329 instances (28.6 per cent.) there was absent or diminished free acid, while in 586 cases (50.8 per cent.) the total acidity was low. These figures closely approximate those shown by the tabulations from the negative glycyltryptophan reactions.

It would appear that Weinstein's contention that his tryptophan test removes the consideration of contaminating saliva as a source of error is not borne out by our study. Further, the presence of negative glycyltryptophan reaction in so large a percentage of extracts with low acidity leads one to the opinion that the significance of the peptidase, said to exist in saliva, as a factor in hydrolyzing glycyltryptophan added to gastric extracts, is quite questionable. This opinion is substantiated by work we have done on saliva, soon to be reported.

Organic Acid.—Ten per cent. of the positive glycyltryptophan tests were associated with the presence of lactic acid. With the exception of one, the cases were carcinoma. Thirty-three negative reactions (3.9 per cent.) were in contents containing lactic acid. Eight and one-third per cent. of the positive tryptophan tests were present in lactic-acid-containing extracts, while 42 (3.6 per cent.) negative tryptophan contents contained lactic acid. It would seem that organic acids have little bearing on the relative variation of the two tests.

Of the entire number of gastric extracts (1175) analyzed in this series, 44, or 3.7 per cent., contained lactic acid by the controlled Uffelmann test. Of the cases proved to be carcinoma ventriculi, lactic acid was present in 25 (28.7 per cent.). As we have shown in these cases, the glycyltryptophan reaction was positive in 31 (35.6 per cent.) and the tryptophan test in 7 (8.04 per cent.). The relatively low percentage of extracts containing lactic acid may be explained on the basis of early diagnosis, many cases being operated on before marked obstruction and retention had developed. Emerson[15] states that in his series of cases of carcinoma ventriculi lactic acid was present in approximately 90 per cent. From our experience, it would appear that the great majority of his cases were far advanced and exhibited marked retention. High mixed organic acidity frequently gives confusing Uffelmann reactions.

It has been held that the *chyle* in gastric extracts vitiates the glycyltryptophan test, but need not be considered when making the tryptophan test. The presence of bile or evidences of tryptic digestion has been used as proof that duodenal contents have been mixed with gastric juice.

The significance of this supposition is shown by analysis of Table 7. The gastric extracts were judged macroscopically as to the presence of bile, and were also tested by means of the Pettenkofer or the fuming nitric acid reaction. It will be seen—(A) That of 110 positive glycyltryptophan reactions, 39 (35.4 per cent.) contained bile; of 1065 negative reactions, 320 (20.4 per cent.) showed bile; of the 24 positive tryptophan tests (B), 10 (41.6 per cent.) were in bile-containing extracts, while 349 (30.4 per cent.) negative tryptophan tests were bile-positive. These figures do not demonstrate that the tryptophan test is uninfluenced by bile in the extracts. It is worthy of note that a relatively high number of both glycyltryptophan and tryptophan reactions are found in bile-containing chyme.

TABLE 7

(A) The Relation of Bile to Glycyltryptophan Test

Groups	Bile Present	Bile Absent
Glycyltryptophan positive...	39	71
Glycyltryptophan negative ..	320	745
Totals..................	359	816

(B) The Relation of Bile to Tryptophan Test

Groups	Bile Present	Bile Absent
Tryptophan positive	10	14
Tryptophan negative	349	802
Totals..................	359	816

The effect of blood, traumatic or "occult," in gastric extracts has at least two points worthy of consideration with regard to the glycyltryptophan and tryptophan tests. Traumatic blood of itself gives a tan or definitely red cast to filtrates. A color reaction such as we are discussing is readily effected by such shades. The second point of note is the possibility of tryptophan resulting from split digestion products of the blood itself, particularly in those cases in which there is marked gastric retention with much flora. Table 8 furnishes interesting data on the above points. In 56 (50.9 per cent.) of the glycyltryptophan positive extracts, blood, traumatic or altered (benzidin test), was present. Of the glycyltryptophan negative extracts, in 236 (22 per cent.) blood was demonstrated. Of the tryptophan positive extracts, 10 (41.6 per cent.) contained blood. In 282 (24.6 per cent.) tryptophan negatives blood was proved. These figures for both tests so closely approximate that it does not seem possible to state that advantage lies with either. The relatively high percentage of positives in extracts containing blood should, however, be borne in mind.

TABLE 8

(A) THE RELATION OF BLOOD TO GLYCYLTRYPTOPHAN TEST

GROUPS	BLOOD PRESENT	BLOOD ABSENT
Glycyltryptophan positive	56	54
Glycyltryptophan negative	236	829
Totals	292	883

(B) THE RELATION OF BLOOD TO TRYPTOPHAN TEST

GROUPS	BLOOD PRESENT	BLOOD ABSENT
Tryptophan positive	10	14
Tryptophan negative	282	869
Totals	292	883

SUMMARY

The work submitted makes apparent the following:

1. In our series more than one-third of the proved cases of cancer of the stomach gave positive glycyltryptophan reactions; more than one-fourth were lactic-acid-positive, and about one-thirteenth of the number exhibited the tryptophan test. Diagnosis of malignant disease of the stomach was in each case quite possible, independent of the above chemic reactions. As a test associated with cancer of the stomach, it will be seen that in our series the glycyltryptophan reaction proved more consistent than tests for common organic or existing free amino-acid (tryptophan).

2. While gastric conditions other than cancer exhibit positive glycyltryptophan reactions, in no single class of disease of the stomach is this test obtained so frequently as in cancer. This fact is of considerable significance chemically, and, perhaps, etiologically. While cancer of the stomach can doubtless be diagnosticated clinically without the glycyltryptophan test, one cannot state that the study of this and allied reactions will prove valueless.

3. Our work does not show that the tryptophan test is, as has been advanced, pathognomonic of cancer.

4. Low free hydrochloric or total acidity is frequently determined in gastric contents exhibiting positive glycyltryptophan, lactic acid, and tryptophan reactions. One cannot state positively

that this diminished acidity is causative. Many cases of low acidity were negative to the above tests.

5. Approximately one-half of the positive glycyltryptophan and tryptophan reactions were in gastric extracts containing bile and blood-elements. Approximately one-fourth of the negative extracts contained blood and bile elements.

REFERENCES

1. Muller: "Zeit. f. klin. Med.," 1889, vol. xvi, p. 496.
2. Fischer: "Deut. Arch. f. klin. Med.," 1902, vol. lxxii, p. 415.
3. Abderhalden: "Zeit. f. physiol. Chem.," 1909, vol. lxii, p. 136.
4. Neubauer and Fischer: "Deut. Arch. f. klin. Med.," 1909, vol. xciii, p. 499.
5. Lyle and Kober: "New York Med. Jour.," 1910, vol. xci, p. 1151.
6. Weinstein: "Jour. Amer. Med. Assoc.," 1910, vol. lv, p. 1085.
7. Warfield: "Bull. Johns Hopkins Hosp.," May, 1911, p. 150.
8. Oppenheim: "Deut. Arch. f. klin. Med.," 1910–11, vol. ci, p. 293.
9. Kohlenberger: "Deut. Arch. f. klin. Med.," 1910, vol. xcix, p. 148.
10. Sanford and Rosenbloom: "Arch. Int. Med.," 1912, vol. ix, p. 445.
11. Weinstein: "Jour. Amer. Med. Assoc.," 1911, vol. lvii, p. 1420.
12. Hall and Williamson: "Lancet," London, 1911, vol. clxxxi, p. 731.
13. MacCarty: "Surg., Gyn., and Obst.," 1910, vol. x, p. 449.
14. Gies: Quoted by Weinstein, "Jour. Amer. Med. Assoc.," 1911, vol. lvii, p. 1420.
15. Emerson: "Clinical Diagnosis," 1906.

THE GLYCYLTRYPTOPHAN (PEPTID) SPLITTING AGENT IN HUMAN SALIVA*

FRANK SMITHIES

Rather more than a year ago Warfield[1] claimed the discovery of a new enzyme in human saliva, "a substance which has the power to split glycyltryptophan" (a dipeptid). This hydrolyzing property of saliva was stated as being lost when saliva is acid or when heated to 100° C. Warfield's report bases his conclusions on the action on glycyltryptophan of 28 specimens of saliva. Of this number, saliva was alkaline (where stated) in all the positive reactions, and acid in all negative glycyltryptophan tests. The use of tobacco, observed in 7 instances, did not materially alter the result, so long as the salivas remained alkaline.

About six months after Warfield's communication Weinstein,[2] in writing of the "tryptophan" test for carcinoma ventriculi, confirmed Warfield's findings. Weinstein's observations are indefinitely stated. The few experiments actually quoted admit of dubious conclusions (*vide* 1 to 3, and A-B). In a foot-note Weinstein states that his colleague, Professor Gies, "although suggesting the probability of ereptic and tryptic excretion by the salivary glands, thinks it possible also that the tryptophan-producing enzyme in mixed saliva is derived in part from the bacteria in the mouth, especially from cavities in carious teeth."

Previous to Warfield's report ptyalin (diastase) had been considered the essential enzyme in human saliva. Maltase can hardly be regarded as distinctive. It would seem that if human saliva contain a proteolytic enzyme, new problems in the physiology of digestion would be presented.

---

* Reprinted from "Archives of Internal Medicine," December, 1912, vol. x, pp. 521-533.

The observations included in this report were made in the endeavor to determine the existence of the peptid-splitting agent in saliva, the nature of this agent, and the conditions under which it might be evidenced.

AUTHOR'S STUDY

Three hundred and thirty-four individuals furnished the specimens of saliva. They were of both sexes, and ranged in age from eighteen to seventy-four years. Three hundred and eighteen specimens came from patients who presented themselves for test-meal examination of gastric function at the Mayo Clinic. Sixteen specimens came from laboratory assistants, nurses, and physicians.

Collection of Saliva.—In the test-meal cases patients were fed the Ewald breakfast. From ten to twenty minutes after they had eaten they were furnished with large test-tubes, into which they spat. They were instructed to furnish saliva, and not nasopharyngeal accumulations or laryngobronchial sputum. The collecting test-tubes had previously been boiled in distilled water, hot-air dried, and plugged with sterile cotton. Saliva was collected for from forty-five minutes to one and one-half hours following the ingestion of the test-meal. It was kept at room temperature in the test-tubes, securely plugged, until the various experiments to be made with it were set up. Except in special instances (*vide infra*), experiments were set up within four hours following the collection of the specimens. The reaction of the saliva was always ascertained with wet litmus at the time the test mixtures were made. In each donor the teeth, gums, and oral, nasal, and pharyngeal mucosæ were inspected.

Routine Procedure for Observation of the Peptid Hydrolyzing Property of Saliva.—For testing the cleavage power of the specimens the dipeptid, glycyltryptophan, was chosen. The preparation made under the direction of Neubauer and Fischer was used. This was obtained in small bottles and preserved under an ample layer of toluol. To guard against the crystallization out of the glycyltryptophan from solution, and the consequent doubtfulness of the results, the preparation was kept in a thermostat at 37° C.

The tests were, in general, set up as follows: Into each of a series of sterile test-tubes (those measuring 10 cm. by 14 mm. were found to answer very well) were poured, respectively, 0.3 c.c of the glycyltryptophan solution, 3 c.c of saliva, and 0.5 c.c of toluol. Sterile pipets were used in measuring the quantities. In each series controls were set up consisting of—(*a*) 0.3 c.c. glycyltryptophan solution + 3 c.c. sterile distilled water + 0.5 c.c. toluol; and (*b*) 3 c.c. saliva + 0.5 c.c. toluol. The tubes were inverted several times to secure complete mixture of the ingredients. They were then placed in a thermostat at 37° C. for twenty-four hours. From each tube was next transferred to each of a set of small test-tubes 2 c.c. of the mixture below the toluol layer. To each tube was then added 0.2 c.c. of a 3 per cent. glacial acetic acid in distilled water solution. The tubes were shaken vigorously. Test for free tryptophan was then made. Bromin vapor was allowed to flow into each test-tube until the glass above its contents showed strong amber. The tubes were next shaken, and note made of any color change occurring in the mixture. The presence of tryptophan was considered proved when the liquid took on lilac, rose-pink, purple, or magenta hues. The color changes were observed by daylight against a white background (filter-paper). By this procedure small amounts of free amino-acid (tryptophan) are readily detected. Questionable reactions were usually due to the presence of very small amounts of tryptophan, dirty saliva, excess of bromin, as when bromin water is used instead of bromin vapor, or poor light.

1. The Presence of Peptid-splitting Agent in Whole Saliva.—In this series of tests a portion of saliva free from food-particles, blood, or nasopharyngeal mucus was examined first for free tryptophan. Reference to Table 1 shows that of 334 specimens of saliva, but 3 showed free amino-acid before the dipeptid glycyltryptophan had been added or the specimens had been incubated. All three positive tests were returned by dirty saliva from individuals with pyorrhœa alveolaris and decayed teeth. One individual had enlarged tonsils with ragged crypts filled with creamy exudate. Of the 3 positive tryptophan tests, 2 occurred in very acid saliva and 1 in neutral saliva (case with foul tonsils).

In this same series portions of the saliva (334 specimens) were incubated with glycyltryptophan under toluol for twenty-four hours, as described above, and at the end of the incubation period were tested for free tryptophan. Table 1 shows the results.

TABLE 1.—THE PEPTID-SPLITTING POWER OF WHOLE SALIVA

No. of Cases	Positive Reactions*			Negative Reactions	Tryptophan Test	Reaction of Saliva	Percentage
	+	++	+++				
148	23	64	52	9	1	Neutral	Pos. 93.9 Neg. 6.1
163	27	79	50	7	2	Acid	Pos. 95.7 Neg. 4.2
23	3	3	13	4	0	Alkaline	Pos. 82.6 Neg. 17.3+
334	53	146	115	20	3		

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++.
Total positive (all degrees) = 314, or 94 per cent.
Total negative (all degrees) = 20, or 5.9 + per cent.

It will be noted that, irrespective of the reaction of the different specimens, 314, or 94.1 per cent., manifested some degree of hydrolytic power for glycyltryptophan. Twenty, or 5.9 per cent., were negative, irrespective of reaction of the saliva. We shall comment on the significance of reaction below. It, however, seems proper here to call attention to the facts that of 334 specimens, 148 were neutral to wet litmus, and that of this number 139 (93.9 per cent.) revealed free tryptophan after incubation. Acid reaction was shown by 163 specimens. Of these, 156 (95.7 per cent.) were capable of splitting glycyltryptophan. Of the 23 distinctly alkaline salivas, 19 (82.6 per cent.) showed free tryptophan after incubation with the test dipeptid. In view of the difficulty in accurately determining shades of difference in reaction between the neutral and alkaline salivas with litmus, we may fairly group the results from such specimens; in other words, of 171 specimens (neutral and alkaline), 154 (90 + per cent.) hydrolyzed glycyltryptophan, with resultant detectable amounts of free amino-acid.

Warfield's tabulation of 28 specimens of saliva shows that in his series 13 were from individuals affected with some form of gastro-intestinal anomaly, while the remainder were from subjects in good health. In 25 specimens (89.3 + per cent.) he obtained cleavage of glycyltryptophan (bromin-water test). He states that all positive reactions were from individuals with alkaline salivas. We are unable to account altogether for the discrepancy between his figures and ours.

2. The Effect of Centrifugalization on the Peptid-splitting Power of Saliva.—Portions of 204 salivas were centrifugalized in a motor-driven centrifuge for sixty minutes. Two c.c. of the top layer of each specimen was mixed with glycyltryptophan and incubated under toluol for twenty-four hours. Table 2 shows in detail the results.

TABLE 2.—THE PEPTID-SPLITTING POWER OF CENTRIFUGALIZED SALIVA

No. of Cases	Positive Reactions*			Negative Reactions	Tryptophan Test	Reaction of Saliva	Percentage
	+	++	+++				
92	39	20	14	19	0	Neutral	Pos. 78.9 Neg. 21 +
106	44	40	7	15	1	Acid	Pos. 85.8 Neg. 14.1+
6	2	1	0	3	0	Alkaline	Pos. 50 Neg. 50
204	85	61	21	37	1		

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++
Total positive (all degrees) = 167, or 81.8 + per cent.
Total negative (all degrees) = 37, or 18.1 + per cent.

Several interesting facts are brought out. It will be observed that, irrespective of the reaction of the salivas, of the 204 specimens, 167 (81.8 per cent.) showed some hydrolyzing power. This is rather more than 12 per cent. less than was exhibited by non-centrifugalized salivas (Table 1). Thirty-seven (18.1 per cent.) specimens were negative. Table 2 also shows that the degree of reaction is less marked than where non-centrifugalized saliva is tested. The majority of the reactions were + or ++ in this series.

The relation of the reaction of saliva to its peptid-splitting power in this series shows interesting variations from that exhibited in Table 1. Of the 92 specimens noted as neutral, 73 (78 per cent.) showed hydrolyzing power, while 19 (21 + per cent.) did not. Of 106 acid salivas, 92 (85.8 per cent.) split glycyltryptophan and 15 (14.1 + per cent.) were unable to do so. Of the 6 distinctly alkaline salivas, 3 (50 per cent.) split the dipeptid. Combining the results returned by alkaline and neutral salivas, we observe that of a total of 98 specimens, 76 (77.5 per cent.) showed hydrolytic power.

In this series of 204 specimens, only 1 (acid in reaction) gave a positive tryptophan test before incubation. This saliva came from a very foul mouth, and contained macroscopic blood and much cellular detritus.

3. Consideration of Relation of Reaction of Saliva to its Peptid-splitting Power.—It is commonly stated that the reaction of saliva is alkaline or neutral to litmus. Using litmus paper moistened in sterilized distilled water, we have found it extremely difficult to determine the finer variations in reaction between weakly alkaline and neutral salivas. Consequently only when there was blue coloration of test-paper in the estimation of at least two observers have we called salivas alkaline. Table 1 shows that of 334 specimens of whole saliva, 171 (51.1 per cent.) were neutral or alkaline. Of these, 154 (90 + per cent.) split glycyltryptophan. One hundred and sixty-three (48.9 per cent.) were distinctly acid to wet litmus. Of these, 156 (95.7 per cent.) were hydrolytic for the test dipeptid.

The number of acid salivas was surprisingly large in view of text-book analyses. We suggest that this high proportion of acid reactions may be due to the conditions of the oral cavities of the donors. Many of our patients were adult or aged peasantry from the northwest United States and Canada. There was a considerable percentage of individuals of European extraction. In many, teeth, gums, and nasopharyngeal anomalies had been entirely neglected. Decayed teeth, pyorrhœa alveolaris, soggy, oozing tonsils, and foul nasal and pharyngeal mucosa were common (*vide infra*). It is also to be emphasized that many salivas came from individuals in poor health (carcinoma or ulcus ventriculi, ulcus duodeni, cachexia from liver, gall-tract, or gastric secretory malfunction, and the like). We have not been able to find in the literature a satisfactory discussion of the influence of disease on reaction or chemic properties of saliva. The observation we present is certainly interesting, and perhaps not altogether unimportant. Of 20 salivas from healthy young adults, 17 (85 per cent.) were neutral in reaction. The time following the ingestion of food in the test-meal cases during which saliva was collected may also have some bearing on its reaction.

4. Consideration of Oral Conditions on the Peptid-splitting Power of Saliva.—*(a) Teeth.*—Notes were made relative to the condition of the donor's teeth at the time that saliva was received from him. The classification in Table 3 needs little explanation. In practically all instances in which teeth were called "poor" or "very poor," there was pyorrhea in addition to dirty, decaying teeth. Some teeth classed as "good" or "fair" also showed pyorrhea. In these and other instances frequently diseased tonsils or foul nasopharyngeal discharge were not lacking.

TABLE 3.—THE RELATION OF THE CONDITION OF THE TEETH TO PEPTID-SPLITTING POWER OF SALIVA

No. of Specimens	Teeth—Condition	Reaction*			
		0	+	++	+++
84	Good	10	35	27	12
50	Fair	6	13	17	14
88	Poor	0	18	28	42
86	Very poor	0	21	18	47
26	Artificial	4	4	5	13

* Degree of reaction: Lilac = +; rose-pink = ++; rose-purple = +++

The interesting features of Table 3 are the following: Of the 334 salivas tested, approximately but one-fourth of the number came from subjects with good teeth, while more than one-half of the specimens were received from individuals with inferior and dirty teeth. From the latter class we never received a saliva incapable of splitting glycyltryptophan, while from 12.5 per cent. of salivas from the good teeth class, the cleavage property of saliva for the dipeptid was not demonstrated. The differences in degree of reaction are striking. In the good teeth class the majority of the reactions are in grades + or ++; while in the very poor teeth groups the preponderance of the reactions fall in grades ++ and +++. Twenty-six (7.5 per cent.) of the salivas in our series came from individuals with artificial teeth. Of this number 15+ per cent. of the salivas did not split glycyltryptophan. These were from clean mouths in 3 instances and from a dirty mouth in a fourth. In this group (artificial teeth) 13 (50 per cent.) of the salivas showed very strong cleavage power. In the majority of these both artificial teeth and patients' mouths were very dirty.

(*b*) *Gums.*—Of 334 individuals, 201 (60+ per cent.) showed erosions at the teeth-gum margins, or definite pyorrhœa alveolaris. Of this number, the saliva was acid in 149 instances (74.1 per cent.). These specimens split glycyltryptophan in 189 instances (94.3 per cent.).

(*c*) *Tonsils and Nasopharynx.*—Salivas were collected from 192 persons in which these parts were inspected. In 53 instances (27.5 per cent.) there was evidence of tonsillar disease (enlargements, crypts, exudate, erosion). In 38 instances (19.7 per cent.) there were evidences of nasopharyngeal inflammation. In 6 instances (3.1 per cent.) there were ulcerative conditions of the oral mucosa, apart from adenoid hypertrophy or pyorrhea.

Of the 192 individuals whose tonsils, oral mucosa, etc., were examined, 73 (38 + per cent.) revealed some abnormality. Of this number 42 (57.5 per cent.) had acid salivas and 31 (42.4 per cent.) of these salivas split glycyltryptophan after incubation for twenty-four hours at 37° C.

(*d*) *The Use of Tobacco.*—Of the 334 specimens of saliva examined, 209 came from males. In 140 instances data were obtained regarding the use of tobacco. Seventy-eight smoked or chewed tobacco or both. Three of these also used snuff. Saliva from these 78 individuals split glycyltryptophan in 69 instances (89.8 per cent.), irrespective of its reaction to litmus. Twenty-five donors chewed tobacco, but did not smoke regularly. Eleven of these had acid salivas. Twenty-two "chewers" donated salivas which split glycyltryptophan in 15 instances (68.1 per cent.).

(*e*) *The Effect of Mouth-washes.*—An aqueous solution of alphozone of 0.4 per cent. strength was used vigorously as a mouth- and tooth-wash in 52 instances. The subjects were directed to hold the solution in their mouths for several minutes, to force it back and forth between their teeth and about the alveolar spaces, and to gargle a portion. The mouth was then rinsed with warm normal salt solution. Saliva was then collected for forty-five minutes. From the 52 donors saliva was alkaline or neutral in 38 instances (73 per cent.) and acid in 14 instances (26.9 per cent.). From this group of 52 specimens cleavage of glycyltryptophan occurred but 17 times (32.7 per cent.). With respect to degree of cleavage, the reaction was in no instance beyond ++.

The results obtained after the use of the strong alphozone solution as a mouth-wash led us to test the effects of it and like solutions on saliva directly, and to experiment with mouth and throat cultures of bacteria.

5. *Consideration of the Effect of Temperature on the Peptid-splitting Power of Saliva.—Boiling.*—A portion of saliva from each of 302 specimens combining all reactions was immersed in a plugged sterile test-tube in water, and kept boiling for thirty minutes; glycyltryptophan solution was added after the saliva had been cooled, and the mixture was then placed under toluol in the thermostat for twenty-four hours. Test for tryptophan was then made in the usual manner. In none of the boiled specimens could free amino-acid be detected.

Room Temperature.—Portions of 160 specimens of saliva were mixed with glycyltryptophan and left under toluol for from twelve to one hundred and twenty hours, at room temperature (about 75° to 80° F.). Table 4 summarizes the result.

TABLE 4.—THE CLEAVAGE POWER OF SALIVA AT ROOM TEMPERATURE

No. of Specimens	Reaction	+ Reaction (Cleavage) after Hours							No. of Specimens Showing No Cleavage
		12	24	36	48	72	96	120	
66	Acid............	3	7	29	16	5	4	0	2
82	Neutral.........	6	30	26	7	9	0	0	4
12	Alkaline........	2	8	0	1	0	0	0	1
160		11	45	55	24	14	4	0	7

Briefly, it is seen that, irrespective of the reaction of saliva, cleavage of the dipeptid occurs in the majority of instances between twenty-four and thirty-six hours after admixture; that in a few instances cleavage may have taken place within twelve hours, or may be delayed ninety-six hours, or no free amino-acid may be detected at the end of one hundred and twenty hours (7 instances); that neutral and alkaline salivas split glycyltryptophan somewhat more rapidly than do acid salivas at room temperature.

Ice-box Temperature.—Thirty-five specimens of whole saliva of the several reactions were mixed with glycyltryptophan under toluol and kept on ice. Portions tested within twenty-four to five hundred and twenty-two hours showed in no instance hydrolyzation of the dipeptid. Of these 35 specimens, after being on ice over five hundred and twenty-two hours, 29 were placed in the thermostat at 37° C., and 26 showed free tryptophan after eighteen hours.

Graded Temperatures.—Specimens of saliva were variously heated in plugged sterile test-tubes, cooled in running water, combined with glycyltryptophan solution, and placed in a thermostat under toluol for twenty-four hours. This mixture, acidulated, was then tested for free amino-acid. Table 5 shows the results.

It is seen that, irrespective of the reaction of the saliva, of 71 specimens examined, there is uniform cleavage up to 60° C. Between 60° and 75° C. there is rapid diminution in peptid-splitting power, varying with reaction somewhat (neutral saliva being most resistant to increased heat). We never had any specimen show cleavage of glycyltryptophan after it had been heated above 75° C. The variations in splitting power of the specimens with different reactions would appear to be somewhat dependent on such reaction, although there may be other factors (thick, clumpy, or dirty saliva).

TABLE 5.—THE INFLUENCE OF GRADED TEMPERATURES ON THE PEPTID-SPLITTING POWER OF SALIVA

No. of Specimens	Reaction of Saliva	Reactions at Temperature												
		20° C.	30° C.	40° C.	45° C.	50° C.	55° C.	60° C.	65° C.	70° C.	75° C.	80° C.	90° C.	100° C.
28	Acid....	25	22	26	23	23	21	22	14	8	1	0	0	0
34	Neutral.	33	31	29	30	26	26	24	22	21	3	0	0	0
9	Alkaline.	9	9	8	7	6	7	5	5	5	0	0	0	0
71		67	62	63	60	55	54	51	41	34	4	0	0	0

6. *Effect of Chemic Solutions on the Peptid-splitting Power of Saliva.*—In these experiments the following solutions were used:

1. Phenol (carbolic acid) in water, 2 per cent.
2. Bichlorid of mercury in water, 1 per cent.
3. Alphozone in water, 0.1 per cent., 0.2 per cent., 0.3 per cent., 0.4 per cent.
4. Antiformin (commercial solution).
5. Absolute alcohol.
6. Acetic acid, glacial.
7. Chloroform.
8. Ferric chlorid solution, 5 per cent.

Procedure.—After specimens of saliva had been tested for free amino-acid and found negative, equal portions were respectively combined with glycyltryptophan solution plus 1 c.c. of the solution of the chemic combination under consideration. Controls of portions of saliva without glycyltryptophan solution and also of the glycyltryptophan solution itself were set up. The tubes were then incubated under toluol for twenty-four hours, when they were made acid, if not already so, with 3 per cent. acetic acid solution and tested for free tryptophan in the usual manner. Table 6 shows the experiments and results in detail.

It will be observed that solutions of 2 per cent. phenol, 1 per cent. $HgCl_2$, antiformin, glacial acetic acid, chloroform, and absolute alcohol, and 0.4 per cent. alphozone absolutely inhibit the peptid-splitting agent in human saliva. A 5 per cent. solution of ferric chlorid prevented cleavage in 88 per cent. of specimens.

TABLE 6.—THE INFLUENCE OF CHEMIC ACTION ON PEPTID-SPLITTING POWER OF SALIVA

No. of Series	No. of Specimens	Combination Tested	No. of Positives	No. of Negatives	Controls: Glycyltryptophan + Saliva		Controls: Glycyltryptophan Alone		Controls: Saliva Alone	
					Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
1	25	2 per cent. phenol + saliva and glycyltryptophan	0	25	23	2	0	25	0	25
2	25	1 per cent. mercuric chlorid + saliva + glycyltryptophan	0	25	25	0	0	25	0	25
3	25	Antiformin + saliva + glycyltryptophan	0	25	21	4	0	25	0	25
4	25	Glacial acetic acid + saliva + glycyltryptophan	0	25	23	2	0	25	1	24
5	25	Chloroform + saliva + glycyltryptophan	0	25	24	1	0	25	0	25
6	25	5 per cent. ferric chlorid + saliva + glycyltryptophan	3	22	24	1	0	25	0	25
7	80	Absolute alcohol + saliva + glycyltryptophan	0	80	74	6	0	80	0	80
8	50	0.1 per cent. alphozone + saliva + glycyltryptophan	32	18	46	4	0	50	0	50
	50	0.2 per cent. alphozone + saliva + glycyltryptophan	24	26	46	4	0	50	0	50
	50	0.3 per cent. alphozone + saliva + glycyltryptophan	11	39	46	4	0	50	0	50
	50	0.4 per cent. alphozone + saliva + glycyltryptophan	0	50	46	4	0	50	0	50

Brief attention may be called to the action of the alphozone solutions. After having conducted the experiments on salivas from individuals who had used alphozone solution as a mouthwash, a few tests (not included in the series of Table 6) carried out in which we used a 0.1 per cent. solution of alphozone combined with saliva was used. Several of the thick, tenacious, or dirty salivas retained good cleavage power for glycyltryptophan, even after so powerful an organic peroxid as alphozone had been added. When the experiments for Table 6 were set up, various strengths of alphozone were added in the attempt to discover the limit at which cleavage of the dipeptid was possible with this admixture. It is seen by Table 6 that only solutions so powerful as 0.4 per cent. alphozone uniformly inhibit the peptid-splitting power of whole saliva, and that diminution in strength of solution results in proportionate increase in the number of salivas which retain that power.

With the exception of the alphozone and chloroform additions to saliva-glycyltryptophan mixtures in our series there were always various grades of precipitation in the combinations when the numerous test solutions were added. It would seem that this fact might seriously interfere with the action of the peptid cleaving agent in saliva, if that agent be an enzyme. Precipitation may not, however, be the only factor. Chloroform and alphozone admixtures produce no marked precipitation in saliva-glycyltryptophan solutions. Chloroform absolutely inhibited cleavage in our experiments. Alphozone solutions only inhibited cleavage of the dipeptid above 0.3 per cent. strength. In addition to the question of increase in alkalinity in alphozone-saliva mixtures, as the percentage of alphozone increases in such solutions one must also consider the importance of alphozone as a germicide. Inasmuch as in our experiments alphozone was the only chemic agent added to saliva which did not cause precipitation of protein, and yet did not invariably inhibit cleavage, its results only can be used to indicate a line of demarcation respecting a factor, at least, in explanation of how saliva splits glycyltryptophan. It is well known that chemicals that precipitate protein in enzyme-containing solutions also inhibit the ferment action of those solutions. Inhibition of the peptid-splitting agent in saliva by such chemic solutions as phenol, mercuric chlorid, antiformin, alcohol, and the like leaves us in doubt as to whether or not such agent was rendered inert by precipitation of an enzyme with protein in saliva or cleavage power was lost by bactericidal action of these strong germicides, or both. Ferric chlorid solutions which precipitate protein in saliva are not very strongly germicidal, apart from mechanic action. In 88 per cent. of specimens cleavage of glycyltryptophan was inhibited by 5 per cent. ferric chlorid solution.

7. *Effect of Bacteria on Cleavage of Glycyltryptophan.*—(*a*) *Saliva + Bacteria.*—Cultures from 27 specimens of saliva were made—(1) In bouillon; (2) on nutrient agar; and (3) on blood-serum-agar. These were allowed to remain three days in the water-bath at 37° C. In reaction the salivas from which cultures were made were alkaline in 3; neutral in 15, and acid in 9.

Table 7 gives details regarding salivas, organisms returned by cultures, etc. At the end of the incubation period experiments were instituted as follows:

Portions of salivas collected during the three days that the cultures were growing and which had been shown to be capable of splitting glycyltryptophan, were heated at 100° C. in a water-bath for one hour. The specimens were then cooled in running water and made neutral with N/10 sodium carbonate. Two series were then made from the specimen: (*a*) Saliva + glycyltryptophan solution + emulsions of bacteria from each set of cultures from saliva. (*b*) Saliva + glycyltryptophan + toluol (controls). The sets were then thoroughly mixed and incubated forty hours at 37° C. Portions of mixtures were then acidulated and tested in the usual way for free tryptophan. Table 7 shows the results.

It is seen that 23 out of 27 salivas which had been rendered incapable of splitting glycyltryptophan by heating to 100° C. are capable of showing some evidences of cleavage power after being mixed with bacteria grown from specimens of saliva. In none of the controls was cleavage power exhibited. In 16 out of the 27 sets free tryptophan was readily recognized on the addition of bromin vapor. In 7 instances there was but a trace of free tryptophan. In 1 instance the result was questionable. In 3 experiments (11.1 + per cent.) no free tryptophan could be detected. The reaction of salivas from which cultures were made appeared to have no great bearing on the results. Very rich flora in such salivas appeared to determine largely the degree of reaction. Rich flora were frequently present from salivas whose donors had very poor teeth or marked pyorrhea, but this was not constant. Nasopharyngeal conditions appeared to have bearing on quantity and variety of bacteria present in salivas.

TABLE 7.—EFFECT OF BACTERIA ON CLEAVAGE OF GLYCYL-TRYPTOPHAN

Series No.	Patient's Number	Reaction of Saliva	Teeth	Organisms in Cultures	Results				Remarks
					Series A Pos.	Series A Neg.	Series B Pos.	Series B Neg.	
1	47285	Alkaline	Good	Streptococci, staphylococci, diplococci, short bacilli.	+	0	0	+	
2	67218	Alkaline	Good	Cocci, lance-shaped bacilli.	0	+	0	+	Adenoids.
3	67232	Alkaline	False	Cocci, diplococci, spirilla.	++	0	0	+	
4	66886	Neutral	False	Diplococci, streptococci, short rods.	+	0	0	+	
5	9596	Neutral	Good	Cocci and short bacilli.	Tr.	0	0	+	Pyorrhea.
6	67244	Neutral	Fair	Cocci, rods and spirilla.	Tr.	0	0	+	
7	67292	Neutral	Good	Staphylococci and streptococci, lance-shaped bacilli.	+	0	0	+	Diseased tonsils.
8	67285	Neutral	Poor	Cercomonas in fresh specimen, cocci, spirilla and rods.	++	0	0	+	Pyorrhea ++
9	67328	Neutral	Good	Diplobacilli, diplococci, staphylococci.	0	+	0	+	Pyorrhea.
10	67352	Neutral	Good	Streptococci and staphylococci, few bacilli.	+	0	0	+	
11	67338	Neutral	Fair	Micrococci, streptococci, staphylococci.	+	0	0	+	Dirty teeth.
12	67368	Neutral	Good	Cocci, lance-shaped bacilli.	?	0	0	+	
13	67336	Neutral	Good	Short rods, cocci, spirilla.	+	0	0	+	Pyorrhea +
14	67342	Neutral	Fair	Cocci, diplobacilli, leptothrix.	Tr.	0	0	+	Large tonsils.
15	67313	Neutral	Good	Micrococci, streptococci, staphylococci, short bacilli.	+	0	0	+	
16	28954	Neutral	Poor	Spirilla in fresh bacilli, diplococci, and streptococci.	++	0	0	+	Many carious teeth.
17	67404	Neutral	Fair	Bacilli and cocci.	+	0	0	+	Several cavities, pyorrhea
18	67365	Neutral	Good	Staphylococci, diplobacilli.	Tr.	0	0	+	
19	67206	Acid	Poor	Diplococcus, streptocociand staphylococci, bacilli.	++	0	0	+	Cavities in teeth.
20	67213	Acid	Good	Streptococci, staphylococci, lance-shaped rods.	Tr.	0	0	+	
21	51204	Acid	Fair	Micrococci, streptococci, rods.	+	0	0	+	
22	67295	Acid	Fair	Staphylococci, streptococci, diplobacilli.	+	0	0	+	
23	57318	Acid	Poor	Streptococci, staphylococci, bacilli, spirilla.	++	0	0	+	Carious teeth.
24	67332	Acid	Very Poor	Staphylococci, streptococci, short bacilli, diplococci, leptothrix.	+	0	0	+	Many stumps and teeth with cavities.
25	67268	Acid	Good	Cocci, diplobacilli.	Tr.	0	0	+	
26	67431	Acid	Good	Cocci, diplobacilli.	Tr.	0	0	+	
27	67371	Acid	False	Cocci, short and long rods	0	+	0	+	

Except as in Table 7, we have made no attempt to determine the exact organisms appearing to have some influence on cleavage of glycyltryptophan, apart from noting the groups returned by cultures from each of the 27 specimens of saliva examined. It would seem, from the considerations of these groups, that symbiosis of the organisms appeared to be responsible for certain ereptic power on glycyltryptophan.

(*b*) *Direct Effect of Cultures of Bacteria from Saliva Upon Glycyltryptophan.*—Transplants from the cultures from the 27 specimens of saliva mentioned above, (*a*), were made on 54 tubes of nutrient agar. These were incubated at 37° C. for forty-eight hours. Growths resulted in all instances, the organisms being streptococci, staphylococci, micrococci, bacilli of varying lengths, diplococci, and a few leptothrices.

To one-half (27) of the tubes was then added 0.5 c.c. glycyltryptophan solution in 5 c.c. warm normal salt solution. To the remaining tubes 5 c.c. normal saline solution alone was added. The tubes were incubated thirty-six hours. At the end of incubation the fluid from each tube was drawn off, and after acidulation each specimen was tested for free tryptophan by bromin vapor. Table 7 gives details regarding the organisms.

Result.—In none of the fluids from culture tubes to which normal salt solution alone had been added was free tryptophan shown. Twenty-one (77.7+ per cent.) of the 27 fluids from cultures where the glycyltryptophan-salt solution had been added showed free tryptophan. The color changes ranged from pale lilac to rich rose pink.

SUMMARY

From the work outlined in this report the following seems apparent:

1. Reaction appears to have little bearing on power of saliva to split glycyltryptophan.

2. Free tryptophan is occasionally met with in salivas from dirty or infected oral cavities.

3. Centrifugalization of saliva lessens its power to cleave

glycyltryptophan. This is rather more marked in alkaline or neutral salivas.

4. Conditions of health and state of oral cavities of donors seem to affect reaction of saliva, with some apparent influence on the peptid-hydrolyzing power of such saliva.

5. Power to hydrolyze glycyltryptophan is lost when saliva is heated above 75° C. The optimum temperature for cleavage is about 37° C. At ice-box temperature cleavage is not carried on, but specimens kept at such temperature for as long as five hundred and twenty-two hours may hydrolyze the dipeptid when incubated subsequently at 37° C. At room temperature cleavage is delayed, but is nevertheless carried on, apparently irrespective of the reaction of saliva.

6. The chewing of tobacco seems to lessen the power of certain salivas to hydrolyze glycyltryptophan. Smoking of tobacco appears to have little effect.

7. The use of strong mouth-washes (*e. g.*, an organic peroxid, as alphozone) results in marked diminution of peptid-splitting power of certain salivas.

8. Strong chemic action on saliva, particularly when the addition of such chemicals causes precipitation of protein, inhibits its glycyltryptophan splitting power. Many such chemic solutions tested in this report were germicides.

Non-protein precipitating germicides (as the organic peroxid group) inhibit the peptid-splitting power of saliva roughly in direct proportion to strength of such solution.

9. Cultures of bacteria grown from salivas may, after salivas have lost their power to split glycyltryptophan (by heating to 100° C.), cause such salivas to split that dipeptid, by admixture with salivas and subsequent incubation.

10. Solutions of glycyltryptophan added directly to cultures of bacteria grown from saliva are readily split, with liberation of free tryptophan.

11. The indefinite nature of any enzyme renders its actual demonstration difficult. While the agent in saliva causing cleavage of the dipeptid glycyltryptophan has certain characteristics of

an enzyme, it would seem that a not inconsiderable factor in such cleavage power is the action of normal or pathologic oral microorganisms, or products of their growth.

REFERENCES

1. Warfield: "Bull. Johns Hopkins Hosp.," May, 1911.
2. Weinstein: "Jour. Amer. Med. Assoc.," 1911, vol. lvii, p. 1420.

THE OCCURRENCE OF TRICHOMONAS HOMINIS IN GASTRIC CONTENTS, WITH A REPORT OF TWO CASES*

FRANK SMITHIES

Since the active Caucasian occupation of the Philippine Islands, the West Indies, and Central America in the last decad, the study of protozoa parasitic in the gastro-intestinal tract of man has received great impetus. New and valuable facts have been brought forward by Musgrave and Clegg,[1] Walker,[2] and others concerning the biology of amebæ and flagellate protozoa, as well as the etiology and symptomatology, when such are present in the human intestinal canal. Following the pioneer work of Dock,[3] of recent years, Freund[4] and Sistrunk[5] have shown that amebæ and flagellate protozoa, which were formerly considered to be present but rarely in the feces of individuals who had never visited tropical regions, are by no means infrequent in the discharges of persons residing in the temperate zone.

With increasing amounts of material available for proper examination it is somewhat curious that the presence of amebæ and flagellate protozoa (particularly Trichomonas hominis) outside the intestines proper has not been more frequently chronicled. A rather close scrutiny of available literature reveals the fact that within the last eight years there has been but one observation detailing the presence of flagellate protozoa in the stomach, esophagus, or oral cavity. In this country and abroad it is quite likely that search for these parasites has not been made apart from intestinal discharges.

Nearly fourteen years ago Skaller[6] reported 2 cases of carcinoma

---

* Reprinted from "Amer. Jour. Med. Sci.," July, 1912, No. 1, vol. cxliv, pp. 82-93. Copyright, 1912, by Lea and Febiger.

at the cardiac end of the stomach, where flagellates similar to Trichomonas vaginalis (Donne,[7] Dock[8]) were discovered in the gastric extracts, as well as in the patient's stools. Shortly afterward Strube[9] recorded a similar case—a male patient, with foul-smelling vomitus and a "hard tumor" in the epigastrium. A few years later Cohnheim[10] described the presence of Trichomonas hominis in a case clinically diagnosticated "gastritis," in the test-meal extract of which the total acidity was 19 and the free hydrochloric acid was estimated at 12, and in a second case clinically carcinoma ventriculi, amebæ were occasionally present. Following Cohnheim, Zabel[11] reported 3 cases where he had demonstrated flagellate protozoa in both gastric and intestinal contents. Two of his cases were diagnosticated achylia gastrica. These had leptothrices, amebas, spirilla, and Trichomonas hominis in the vomitus, gastric washings, and the stools. The third case was one of carcinoma of the stomach, at first with slight interference with motility, but later with marked retention and the presence of lactic acid. Megastomum entericum was demonstrated in the gastric extracts. Cohnheim[12] shortly after stated that he had seen Cercomonas hominis and Trichomonas hominis in cancerous involvements of the tongue and esophagus, and also in the mouths of individuals with carious teeth. This observation was verified by von Leyden.[13] So far as we have been able to discover, the most complete study of flagellates in gastric extracts has been made by Rosenfeld.[14] He comments upon the fact that Trichomonas hominis has been reported usually in extracts that show achylia, but claims that this does not necessarily follow, inasmuch as one of his cases had a free hydrochloric estimation of 6 and a total acidity of 37. Rosenfeld describes 6 instances of the presence of Trichomonas hominis in gastric contents, where carcinomas involved various positions in the wall of that viscus. They were frequently accompanied by long bacilli (Boas-Oppler) and leptothrix. The number of flagellate protozoa increased in proportion to the diminution of acidity and as retention progressed. All Rosenfeld's patients exhibited cachexia and palpable tumor in the epigastrium.

We have not been able to discover a report of the finding of Trichomonas hominis in gastric extracts outside of Continental literature. Perhaps a routine search for this parasite has not been made in gastric contents. Observations upon its occurrence in the stools of patients living in the northern half of the United States are rapidly becoming more numerous, as the recent study of Sistrunk[15] demonstrates. It would seem timely to place on record somewhat fully the following 2 cases where trichomonads were demonstrated in gastric extracts. Search for this and other parasites in gastric contents may thereby be stimulated.

CASE REPORTS

CASE 1.—Mrs. G., aged twenty-eight years, a native of the mineral-well district of Texas, was referred by Professor Aldred Scott Warthin, Ann Arbor, Michigan, August 17, 1908.

Subjective Symptoms.—Severe headaches, coming on paroxysmally, especially following exertion, excitement, etc.; attacks of "dyspepsia," namely, nausea, belching of gas, with "sore stomach," obstinate constipation, and general weakness.

Family History.—Negative.

Personal History.—Was a healthy child, raised in southern Texas, married at sixteen, a widow at nineteen. Was operated upon at that time for "ovarian trouble"; made a good recovery, and then commenced the study of nursing at Dallas, Texas. Later, had her appendix and one ovary removed. She overworked at the nurses' training-school and had a "nervous breakdown" when aged twenty-four years. Was again married a year later, although she was not well at the time, complaining of "sore stomach," dyspepsia, and weakness. She was nauseated constantly, but never vomited. Habitual constipation resulted in hemorrhoids, which required several operations before she became comfortable. At these operations she lost much blood. The hemorrhoids bled especially freely again in the spring of 1908. Menstruation has been generally regular; patient never pregnant, never passed clots, nor had leukorrhea. No urinary symptoms.

The present trouble dates back about two years. The main symptoms have been loss of appetite, nausea, distress after eating a hearty meal, belching of gas, severe prostrating headaches, and weakness. The headaches are most frequent and severe when the "dyspepsia" is most troublesome and when constipation is marked.

The patient has lost 10 pounds in weight during the last nine months. Constipation has been relieved by raw fruit and fresh vegetable diet and large drafts of a Texas mineral-well water, not boiled.

Examination.—Temperature, 98.8° F.; pulse, 68; respiration, 22 (3 P. M.).

Patient of medium build, with moderate amount of panniculus; skin pale, sallow throughout, but not jaundiced; sclerotics and mucous surfaces pale, but not jaundiced; tongue has a moderately heavy, grayish yellow, adherent coat; breath heavy.

Mouth, nose, and throat negative. Reflexes negative. Thorax negative.

Abdomen slightly distended; navel above the level of the ribs. Slight tenderness in right iliac fossa; both kidneys easily palpable; liver and spleen negative. Rather marked gurgling throughout entire abdomen; splashing sounds on tapping between navel and pubis. On inflation, stomach holds 28 bulbs without discomfort; the lesser curvature distinctly seen at one fingerbreadth above the navel in the midline, while the greater curvature is made out at four fingerbreadths below the navel in the median line.

Pelvis: Right ovary and tube removed; left ovary free; uterus in good position and free; pelvic floor moderately strong; external genitalia negative (Dr. Frank Witter).

Blood.—Red blood-corpuscles, 4,500,000; white blood-corpuscles, 6210; hemoglobin, 95 per cent. Differential formula (350 white cells counted): Small lymphocytes, 11.14 per cent.; large lymphocytes, 4.6 per cent.; transitionals, 0.57 per cent.; polymorphonuclears, 74.5 per cent.; eosinophile polymorphonuclears, 1.7 per cent.; myelocytes, 0.28 per cent.; mast-cells, 0.28 per cent.; degenerates, 5.1 per cent.

Urine: Negative, chemically; no parasites seen.

Gastric Examination.—Test-meals.

August 19th: Shredded wheat biscuit meal removed after forty-five minutes. Light yellow, gastric odor, particles well broken up; 65 c.c. recovered; lavage clear after 2 liters of water.

Chemic examination: Total acidity, 40; free HCl, 30; Uffelmann and organic acid absent.

Microscopic examination: Numerous very active, flagellate protozoa, the majority with "ground-glass" appearing bodies; a few sluggishly moving and darker. In warm preparations, four anterior flagellas discernible; undulating membrane seen with difficulty. The organism was recognized as Trichomonas hominis and demonstrated as such to several colleagues. Many motile and non-motile bacilli. Few meat-fibers well broken up; starch, erythrodextrin.

Pepsin and rennin reduced. Occult blood—negative (guaiac and old turpentine method).

August 20th: Shredded wheat biscuit meal; removed sixty-seven minutes after eating; 73 c.c. recovered; lavage clear after 3 liters of water. Extract, light yellow, gastric odor; test food well broken up.

Chemic examination: Total acidity, 45; free HCl, 20; Uffelmann, Pettenkofer's, organic acids, and occult blood absent.

Microscopic examination: Few short non-motile rods; no flagellate protozoa or amebas seen; slight microscopic food retention.

Pepsin and rennin present, but reduced.

August 21st: Shredded wheat biscuit meal removed thirty-five minutes after eating; 40 c.c. recovered; light yellow, gastric odor; mucus in slight excess. Lavage and test-meal fluid, warm normal saline solution.

Chemic examination: Total acidity, 18; free HCl, 6 (doubtless not accurate on account of normal salt being administered with test food). Uffelmann, Pettenkofer, organic acid, and occult blood absent.

Microscopic examination: Enormous number of very actively motile trichomonads seen. Many dying and dead forms, some coarsely granular and some vacuolated. In some, when the preparation was diluted with warm saline solution, undulating membranes well discernible. The trichomonads appear smaller than those seen in this patient's stool (see below), but are quite as motile. As nearly as could be estimated the average length of the body was about 12 microns. No measurements of the tails were made. Specimens were kept on the warm stage the greater part of the morning, and with the frequent addition of warm saline solution, actively motile forms were preserved. Cold or warm, acid and alkaline solutions rapidly killed the flagellates (hydrochloric acid above 0.3 per cent.; acetic acid, nitric acid, caustic soda, caustic potash, 1 per cent. lactic acid, 0.5 per cent. 1 per cent. salicylic acid, and carbolic acid solutions were used). When the gastric extracts were diluted with anilin dye preparations (methylene-blue, Gram's mixture, gentian violet, Wright's stain) in an attempt to stain the organisms, the smears showed small, contracted, scarcely recognizable dead organisms. Tubes of blood-serum and glucose agar inoculated with 5 drops of gastric extract, in which actively motile trichomonads were present in large numbers, revealed not even recognizable dead organisms the following day, although there was an abundant growth of bacilli. In the gastric extract itself incubated in three volumes of normal saline solution no trichomonads could be made out after twenty-four hours.

August 22d: Fasting stomach; patient tubed at 8.25 A. M. No contents obtained. Lavage with warm normal saline solution was clear, with the exception of small amounts of mucus. In the examination of 7 specimens of the lavage water and bits of mucus, only 1 trichomonad was seen. This was found in a bit of dense mucus and was not motile, even though the preparations had been kept warm since they were secured.

August 22d: Riegel dinner removed at 4.45 P. M., 160 c.c. recovered. Lavage clear after 4 liters of warm saline solution. Extract showed, macroscopically, much poorly chewed food.

Chemic examination: Total acidity, 16; free HCl, 8; Uffelmann, Pettenkofer, organic absent; occult blood, faint positive (guaiac and old turpentine method).

Microscopic examination: Several small, granular, sluggishly motile trichomonads seen; flagellas very difficult to observe, even with subdued light. Many long, slender, non-motile bacilli, usually in pairs. Food débris in various stages of digestion; mucus in excess.

Examinations of Stools.—August 22d: Large, greenish-brown stool following 1 ounce of domestic Carlsbad salts. Stool has peculiar foul, penetrating, musty odor. Much partly altered food and mucus, in tenacious strings and flakes. Reaction alkaline to litmus.

Chemic examination: Skatol, positive. Occult blood, faintly positive.

Microscopic examination: Enormous numbers of large (15 to 22 microns approximately), actively motile trichomonads; no amebæ; great numbers of long, slender, motile and non-motile bacilli; much food débris, poorly digested; mucus in excess.

Progress of the Case.—The following treatment was suggested: Hydrargyri chloridum mite, 5 grains, in divided doses, at bedtime, followed by 1 ounce of salts before breakfast the following morning. This medication was given twice weekly, and the stools were saved after each bowel movement. Acidum hydrochloricum dilutum was given in doses of 30 drops a half-hour after meals, and repeated an hour and a half after each meal. Gastric lavage on empty stomach, with large quantities of 1 per cent. sodium salicylate solution, was carried out three times weekly. Intestinal diet and boiled water were ordered.

After the patient had had two "rounds" of calomel and salts and several lavages of salicylate of soda, trichomonads were no longer present in either gastric contents or stools. Flatulence, nausea, headaches, and weakness disappeared. The patient felt so well that in late September a trip to Canada was allowed. On October 3d she again reported, saying that she felt well, although she had not been under treatment while away from Ann Arbor. A specimen of gastric contents showed no flagellate protozoa. A fresh stool, examined after Carlsbad salts had been administered, showed enormous numbers of motile bacilli, much mucus, and many triple phosphate crystals. Examination of four fresh preparations on the warm stage revealed one large, very actively motile trichomonad.

On October 6th the patient was given 50 grains of thymol, in two doses, at bedtime, combined with 2 grains of calomel. At 7 A. M. the following morning an ounce of Carlsbad salts was administered. The stool was foul smelling, and contained much poorly digested food, but few motile bacilli and no trichomonads were seen.

The patient went South on October 10, feeling very well. Her physician was advised regarding the condition present, and with his aid treatment was carried out along the above lines. The last time information was received from the patient (spring, 1910) she was in excellent health, had gained weight, and had had no further return of protozoa in either gastric extracts or stools.

CASE 2.—Mrs. J., aged forty-seven years, native of Michigan; referred by Dr. F. N. Bigelow, Holly, Michigan, April 20, 1909.

Subjective Symptoms.—Feeling of weight high in epigastrium, immediately after eating; "sourness" of stomach, with bitter eructations; flatulence; obstinate constipation; very annoying cough; facial neuralgia; palpitation of heart; nervousness.

Family History.—Sister died of pulmonary tuberculosis; otherwise negative.

Personal History.—Good health until four years since. Never pregnant.

Present Trouble.—About four years ago had stomach disturbances, which were diagnosticated "dilatation and fermentation"; suffered from chronic constipation and hemorrhoids; had a Whitehead operation performed for the hemorrhoids, and at that time lost a great deal of blood, with resultant weakness. After operation, the trouble appeared to improve. The patient *spent the last three winters in Florida.*

In the fall of 1908 had bronchopneumonia; convalesced in Florida; improved slowly; developed "whooping-cough," which was so severe that vomiting frequently occurred, especially at night. Has been losing appetite, strength, and weight during the last six months. Recently developed distressing sense of weight high in the epigastrium, most marked immediately after eating, with acid eructations and regurgitation of but slightly altered food; character of food makes little difference in this respect; the eructations frequently last for two hours after meals, and are worse when lying down; vomiting relieves. Of late constipation has become very obstinate, requiring strong cathartics. When constipated, neuralgia and nervousness are aggravated.

Examination.—Temperature, 99° F., respiration, 36; pulse, 92 (4 P. M.).

A moderately large, thick-set woman, of asthmatic type; appreciable cyanosis of tip of nose, ears, and of lips; coughs frequently and paroxysmally, cough having a slight "brassy" ring; sclerotics slightly injected.

Tongue heavily coated; throat—"marked enlargement, of true aneurysmal type, of the ascending pharyngeal artery, from the level of the larynx to just above the orifice of the Eustachian tube; the vessel shows marked pulsation throughout the entire field of observation" (report of Professor R. Bishop Canfield).

Neck: Marked carotid pulsation on right; no tracheal tugging or positive venous pulsation.

Thorax: Diffuse bronchitis, more marked in left lower back; moderate cardiac hypertrophy. Blood-pressure: Systolic, 145; diastolic, 104 (Riva-Rocci, 12 cm. cuff).

Abdomen: Distended and tympanitic; gurgling sounds throughout; stomach by inflation extends two fingerbreadths below the navel in the midline; tenderness high in the epigastrium and over the gall-bladder.

Radiogram: Moderate cardiac hypertrophy; great vessels negative; pulmonary edema; "dilated esophagus" (Dr. V. J. Willy).

Urine: Trace of albumin in twenty-four-hour sample (acetic and ferricyanid test).

Sputum: "Curschmann's spirals"; few alveolar cells containing blood-pigment.

Blood: Red blood-corpuscles, 4,560,000; white blood-corpuscles, 5240; hemoglobin, 90 per cent. Differential formula (516 white cells counted): Small lymphocytes, 9.7 per cent.; large lymphocytes, 3.1 per cent.; transitionals, 6.4 per cent.; polymorphonuclear neutrophiles, 66.8 per cent.; eosinophile polymorphonuclears, 2.4 per cent.; myelocytes, 0.5 per cent.; degenerates, 10.8 per cent. No atypical red cells.

Gastric Examination.—April 28th: Test-meal: Shredded wheat biscuit and distilled water; removed seventy minutes after eating. Stomach-tube passed with difficulty on account of enlarged vessel in throat; patient vomited 80 c.c. of partly altered test-meal food chiefly before tube passed into stomach; 40 c.c. of a canary-yellow fluid removed through tube; the latter contained an excess of mucus, together with well-broken-up food, and had a very sour odor.

Vomitus: Straw colored, slightly sour odor; shredded wheat biscuit poorly broken up; Congo and Günzberg test faintly positive.

Chemic examination: Total acidity, 4; free HCl, 4; occult blood, organic acid, and Pettenkofer absent.

Microscopic examination: Poorly digested shredded wheat biscuit; one sluggishly moving, flagellate protozoön, with granular endoplasm; many motile bacilli.

Gastric extract—chemic examination: Total acidity, 56; free HCl, 18; Uffelmann, Pettenkofer, occult blood (guaiac and hydrogen dioxid test), and organic acid absent.

Microscopic examination: Many rather small (average about 8 microns), granular appearing, sluggishly motile trichomonads; many globular, vacuolated, and contracted forms, apparently dead; many leukocytes and cell nuclei; enormous numbers of actively motile, long, and slender bacilli; food-particles, potato starch, shredded wheat biscuit fibers, few meat-fibers well preserved, mucus in marked excess.

Digestion: Pepsin and rennin present, but greatly diminished.

May 1st: Fasting stomach; patient tubed at 9.15 A. M.; 45 c.c. canary-yellow fluid removed, mixed with shaggy strips of mucus, bits of hard egg, and toast; lavage with warm normal saline solution, clear after about 3 liters. Some of the first contents recovered appeared to come from the esophagus and were Congo negative.

Chemic examination: Total acidity, 22; free HCl, 14; Uffelmann, occult blood, and organic acid tests negative. Pettenkofer, faintly positive. Pepsin and rennin—trace.

Microscopic examination: Few slightly motile, darkly granular trichomonads; many ovoid, balloon-shaped, and globular forms, exhibiting coarse endoplasm, frequently with large vacuoles; many short, non-motile bacilli, single and in chains of from 4 to 6; cell nuclei increased; much mucus and microscopic food retention. This patient was not given a Riegel dinner at this time on account of the danger of tubing due to the aneurysm of the ascending pharyngeal artery.

Stool Examinations.—April 29th: Fresh specimen secured after administration of 1 ounce of domestic Carlsbad salts on empty stomach. Large, greenish yellow, foamy, semifluid stool, with penetrating, acrid, and musty odor; large strings of mucus mixed with small particles of food remains.

Chemic examination: Indol and skatol positive; occult blood positive (guaiac and hydrogen dioxid test).

Microscopic examination: Enormous numbers of very actively motile, generally pyriform trichomonads. The majority had finely granular bodies, and were uniformly larger than those seen in the gastric extracts of the day previous and subsequently. Some were very large, measuring from 20 to 28 microns. With subdued light, and when the protozoa were dying or entangled in mucus or food débris, four anterior flagellas and the undulating membranes could be made out. On the warm stages specimens were kept the greater part of a forenoon, before they became sluggishly motile, coarsely granular, contracted, or large and vacuolated, preceding their death. Attempts were made to obtain stains by the carmin and the osmic acid Wright stain methods (as elaborated by Freund under Professor Dock's direction at the University Hospital, Ann Arbor), but with no success. The cell bodies appeared to become disintegrated in the drying and fixing, so that only poorly stained débris showed. Probably greater experience with these methods would have led to more satisfactory results. Attempts at culture in the following media were made: (1) Human blood mixed with mucus from feces which had been previously washed in warm normal saline solution; (2) bouillon mixed with blood-serum; (3) normal saline solution alone; (4) 0.5 per cent. lactic acid; 5 per cent. blood-serum in normal saline solution; (5) solutions of 5 per cent. and of 10 per cent. ox bile in sodium citrate in normal saline solution; (6) ox bile alone;

(7) 5 per cent. ox bile and 5 per cent. blood-serum, with 0.5 per cent. lactic acid in normal saline solution; (8) 5 per cent. ox bile, 5 per cent. blood-serum in beef bouillon; (9) alkaline saliva. All methods were unsuccessful. Cold water or salt solution, or these above 110° F., rapidly caused death of the trichomonads. Solutions of organic and inorganic acids (markedly acid to litmus) and of alkalis (markedly alkaline to litmus) caused rapid disintegration of the parasites.

In the stool, in addition to the flagellates, were vast numbers of actively motile bacilli. There was much poorly digested food and mucus.

May 1st.—Stool passed without cathartic. Medium size, in flat ribbons, soft, coated with mucus; of penetrating, musty odor.

Chemic examination: Occult blood and indol negative. Schmidt's bichlorid test, bilirubin.

Microscopic examination: No trichomonads in either liquid parts of stool or in bits of mucus, although 9 specimens were examined carefully; many motile bacilli; much poorly digested food.

Treatment.—This case was treated similarly to Case 1, with the exception of frequent lavages. A preliminary lavage with 1 per cent. solution of sodium salicylate was given; after that "rounds" of calomel and salts, with doses of hydrochloric acid after meals. Frequent small feedings with intestinal diet relieved the epigastric distress, the regurgitations, and the flatulence. A sedative controlled the coughing by lessening the arterial pulsations that constantly tugged at the larynx.

On June 3d the patient felt very well, had no gastric or intestinal protozoa, and returned home. She was seen again, with Dr. Bigelow, in the fall of 1910. Exposure while on a camping trip had brought on cough and some return of old symptoms in the stomach. The esophagus and gastric extracts showed no flagellate protozoa. The stools exhibited many sluggishly motile trichomonads, numerous motile bacilli, and an excess of mucus.

The patient was given a preliminary treatment of calomel and salts, and when the intestinal tract was well emptied, had 60 grains of thymol administered in two doses at bedtime. This was followed by a saline cathartic the following morning. The stool showed no flagellate protozoa and few motile bacilli. The patient returned home under treatment and has not been heard of since.

Inasmuch as the above cases have been considered in detail clinically, but little further comment appears necessary. However, it would seem proper briefly to emphasize certain facts.

Both patients were women who had resided in semitropical climates; both had been weakened by illness and loss of blood incident to surgical procedures; both patients had habitually partaken of unboiled water from surface wells, and had doubtless also eaten freely of fresh, moist, green vegetables and fruit in all probability contaminated. Neither patient had experienced periodic or chronic diarrhea; on the contrary, obstinate constipation was present in spite of the existence of enormous numbers of flagellate protozoa and motile and non-motile bacteria in the intestinal tract. This is somewhat unusual where trichomonads are present, but the condition has also been observed by Freund[16] (Case VII, his series) and others. In each case gastro-intestinal symptoms were prominent. These were nausea, flatulence, abdominal distention, colicky pains, and constipation. Skatol and indol were present in the stools, and so-called "intoxication symptoms," as headaches, neuralgia, and exhaustion, were observed. The blood showed slight anemia, with increase in eosinophiles and degenerated leukocytes.

The test-meal revealed microscopic retention—lowered total and free hydrochloric acid (shredded wheat biscuit meal), as well as increased amount of mucus containing great numbers of bacteria and trichomonads. The stools were the characteristic greenish-brown, semiliquid variety of protozoan infection after Carlsbad salts have been administered. Bits of mucus, occasional altered blood, rich flora, and partly digested food were concomitant with the large numbers of Trichomonas hominis.

In these patients one can only surmise the source of the infection of the esophagus, stomach, and intestines by the flagellates. It may be that the finding of the protozoa in the esophagus and stomach was secondary to a primary focus in the duodenum and jejunum, the organisms passing upward through insufficient sphincter pylori. It seems probable also that the trichomonads were ingested with food and water. Some of them, protected by mucus in the lower esophagus and in the stomach, may not have been immediately killed by the acid gastric secretion.

Food and water may be contaminated readily in a great many ways. Flagellates may exist in the sputum of patients with tonsillar or nasal abscess (Leuckhart[17]), or in sputum from non-tuberculous lung cavities, for example, bronchiectasis (Litten,[18] Lenhartz[19]), or when individuals are affected with markedly carious teeth (von Leyden,[20] Prowazek,[21] Theobald[22]) or oral cancer (Cohnheim). Dock[23] has mentioned the finding of trichomonads in the discharges of snails, frogs, and ducks. The stools of patients affected with typhoid fever, amebic dysentery, cholera, or enteritis, primary or secondary to malignant disease of the stomach or bowel, may be rich in trichomonads (Dock,[24] von Jaksch,[25] Epstein,[26] Davaine,[27] Grassi,[28] May,[29] and others). Hunt[30] has reported the finding of flagellates in perineal abscess; Cunningham[31] noted their presence in a case of abscess of the liver. As Dock[32] has observed, the presence of trichomonads in urine may be responsible for wide dissemination. The possibility of resistant spore forms of the flagellates explains their viability under adverse conditions.

Morphologically, the parasite seen in the 2 cases here reported differs very little from the classic picture of Trichomonas hominis as established by Donne[33] and Dock.[34] Inasmuch as the protozoa described by these and other observers and ourselves showed four anterior flagellas, together with an undulating membrane, it would seem that the "new" form of trichomonas recently described by Alexieff[35] conforms only to type. It might be observed that the trichomonads seen in the gastric extracts in our cases were approximately but half as large as those found in the stools of the same host. They seemed less resistant to external influences, but in other respects resembled the larger variety.

The cases presented contribute no facts regarding the much debated question of Trichomonas hominis as an etiologic factor. Certainly its removal in quantity from the gastro-intestinal tract of its host is attended by clinical benefit. It has been advanced frequently that the presence of great numbers of flagellates acts as a mechanic irritant to the intestinal mucosa or that such protozoa secrete a substance which is irritant. While these observations may be true, we feel that other factors might be considered.

The rapid multiplication of intestinal bacteria and protozoa (as trichomonads) results in a great quantity of protein-containing flora in all stages of viability. In the life-cycle of the trichomonas dead forms necessarily result. What action succus entericus or associated bacteria and the like have toward hastening this death we are not prepared to state. The dead forms impose upon the digestive juices an excess of protein ("foreign proteid") for cleavage. As the work of Vaughan[36] and his associates has shown, this protozoic protein can be considered homologous to any other protein, chemically. The hydrolyzation (cleavage) of this protein by digestive ferments or associated bacterial enzymes results in the production of so-called "toxic" and "non-toxic" groups. These may be further split into amino-acids or simpler radicles. It is suggested, in view of these facts, that these cleavage products of the protein contained in the flagellates may be a not inconsiderable influence either as—(1) A gastro-intestinal irritant; (2) a factor in altering metabolic change in digestive glands; (3) a source of so-called "intoxication symptoms" clinically.

REFERENCES

1. Musgrave and Clegg: Publications of the Government Laboratories, Manila. P. I., 1904, 93; "Philippine Jour. Sci.," Manila, 1906, vol. l, p. 909; *ibid.*, 1908, vol. iii, p. 77.
2. Walker: "Jour. Med. Research," 1907, No. 7, p. 379.
3. Dock: "Texas Med. Jour.," April, 1891.
4. Freund: "Arch. Int. Med.," 1908, vol. i, No. 1, p. 28.
5. Sistrunk: "Jour. Amer. Med. Assoc.," 1911, vol. lvii, p. 1507.
6. Skaller: "Berlin. klin. Woch.," June, 1898, p. 551.
7. Donne: Compt. rend. de l'Acad. des Sci., 1836, vol. iii, p. 385.
8. Dock: "Amer. Jour. Med. Sci.," January, 1896, pp. 1–24.
9. Strube: Berlin. klin. Woch.," 1898, No. 32, p. 708.
10. Cohnheim: Deut. med. Woch.," 1901, No. xxvii.
11. Zabel: Arch. f. Verdauungskrankh.," 1901, vol. vii, p. 509.
12. Cohnheim: "Deut. med. Woch.," 1902, p. 174.
13. Leyden: *Ibid.*, 182.
14. Rosenfeld: *Ibid.*, 1904, vol. xxx, p. 1717.
15. Sistrunk: *Loc. cit.*
16. Freund: *Loc. cit.*
17. Leuckhart: Die Parasiten des Menschen, 2. Aufl., vol. l, p. 315.
18. Litten: "Beit. z. Zentralbl. f. klin. Med.," 1886, No. 5, p. 69.

19. Lenhartz: "Mikroskopie und Chemie am Krankenbette," p. 61 (Dock).
20. Leyden: *Loc. cit.*
21. Prowazek: "Arch. f. Parasitenkunde," 1902, p. 166.
22. Theobald: "Centralbl. f. Bakteriologie," 1904, p. 86.
23. Dock: *Loc. cit.*
24. Dock: *Loc. cit.*
25. Jaksch: "Wien. klin. Woch.," 1888, vol. xxv, p. 511.
26. Epstein: "Präger med. Woch.," 1893, No. 38, 40.
27. Davaine: "Compt. rend. de la Soc. de Biol.," Paris, 1854, vol. i, p. 129.
28. Grassi: "Zeit. f. klin. Med.," Berlin, 1897, vol. xxxi, p. 442 (Janowski).
29. May: "Arch. f. klin. Med.," 1892, vol. xlix, p. 51.
30. Hunt: "Lancet," London, July, 1906, 28.
31. Cunningham: "Quart. Jour. Microscopic Sci.," 1881, vol. xxi, p. 234.
32. Dock: *Loc. cit.*
33. Donne: *Loc. cit.*
34. Dock: *Loc. cit.*
35. Alexieff: "Compt. rend. Soc. de Biol.," Paris, 1909, vol. lxvii, p. 712.
36. Vaughan, Cumming, and McGlumphy: "Zeit. f. Immun. und exp. Therapie," May 13, 1911, vol. ix, No. 4.

GASTRIC ULCER WITHOUT FOOD RETENTION

A CLINICAL ANALYSIS OF 140 OPERATIVELY DEMONSTRATED CASES*

FRANK SMITHIES

To July 1, 1912, there had been 1341 operations performed for ulcer of the stomach and duodenum in the Mayo Clinic. Of this number, 404 were proved to be ulcers of the stomach. In 264 (65.3 per cent.) of these gastric ulcers there was definite food retention demonstrable after twelve hours by the raisin and cooked rice test (Strauss, Hansmann). In 140 (34.6 per cent.) of these operatively proved gastric ulcers no food retention was evident.

The diagnosis of surgical gastric and duodenal ulcer with food retention is comparatively simple, but the recognition of gastric ulcer where the stomach's emptying power is still unimpaired offers much greater difficulties. While careful development of the history, routine physical examination, and scrutiny of test-meal and laboratory data frequently admit of tentative diagnosis of gastric ulcer, a large number of cases present a picture so blurred by duodenal, gall-bladder, and appendiceal manifestations that unreserved diagnosis is rare.

This report has been made in the endeavor to determine the possibility of exact prelaparotomy diagnosis of the above-mentioned group of cases.

Material.—The analysis covers 140 cases of proved gastric ulcers, without food retention, from the services of W. J. and C. H. Mayo.

---

*Reprinted from Amer. Jour. Med. Sci., 1913. Submitted for publication October 15, 1912. Copyright, 1913, by Lea and Febiger.

Age.—Table I indicates that the largest number occurred between fifty and sixty years of age (28 per cent.). Ninety-two per cent. of all cases were between the ages of thirty and sixty.

TABLE I

Age	No. of Cases	Per Cent.
0–10	0	0.0
10–20	0	0.0
20–30	21	15.0
30–40	38	27.2
40–50	31	22.2
50–60	39	28.0
60–70	8	5.1
Over 70	3	2.1

Sex.—In this series there were 103 males (73.6 per cent.) and 37 females (22.4 per cent.), or approximately 3 males to each female. Table II shows the number of each sex at different decads. Fifty-seven per cent. of the ulcers in women occurred between the ages of forty and sixty. In these two decads occurred 47 per cent. of the ulcers in males. No case occurred in females after the sixth decad.

TABLE II

Years	Males	Females	Total
0–10	0	0	0
10–20	0	0	0
20–30	14	7	21
30–40	29	9	38
40–50	25	6	31
50–60	24	15	39
60–70	8	0	8
Over 70	3	0	3

Nationality.—American born, 98 cases. The remainder were largely Swedish, Irish, and Canadian.

Occupation.—A widely diversified range of occupation was exhibited. In the list were 46 farmers (32 per cent.), 5 physicians, 2 stone-cutters, 2 blacksmiths, 2 miners, and 1 brickmaker.

Habits.—The histories indicate that ulcers occurred in 46 (32 per cent.) individuals using alcohol. In 10 there were evidences of its excessive use. Five of the cases were heavy smokers.

Dietetic Errors.—No definite data with respect to this feature are available. The occupational statistics may be suggestive.

Previous Infectious Diseases.—A history of typhoid fever was obtained in 26 (18.9 per cent.). Pneumonia was noted in 6; scarlet fever, in 8; measles, in 8; syphilis, in 5; gonorrhea, in 6; la grippe (severe), in 4; rheumatism, in 3; diphtheria, in 2; smallpox, in 2; and malaria, in 8.

In 2 cases there was nephritis; in 1, cirrhosis of the liver.

Twelve (8.5 per cent.) had previously been operated on for appendicitis and 2 for gall-stones. These figures are instructive, taken into consideration with the extragastric operative findings (*vide infra*).

Anemia.—Where specifically noted, the hemoglobin averaged 72 per cent. (Dare).

Nutrition.—In 97 of the 140 cases definite figures were available respecting loss of weight. The minimum loss was 5 pounds; the maximum, 65 pounds. The average loss was 20.5 pounds; The rate of loss varied. In some cases patients were not aware of loss until weighed in the examining-room. Other patients had lost weight rapidly—*e. g.*, 65 pounds in six months; 30 pounds in six weeks; 25 pounds in six weeks; 20 pounds in five weeks; 25 pounds in three weeks, etc. Even rapid loss of weight was rarely associated with cachexia, usually evident in malignant disease. Night pain, with loss of sleep; constant pain, with fear of aggravation on eating, and caution in diet on account of recent hemorrhage, were prominent factors associated with rapid loss of weight.

Twelve cases showed progressive *gain* in weight; 21 had neither lost nor gained.

Appetite.—In 52 the appetite was noted "poor"; in 52, "fair"; and in 36, "good." Frequently the appetite is lost in acute attacks of pain or distress. The dread of bringing on distress by food ingestion sometimes causes a poor appetite habit. The same may be said of persistent "dieting."

Bowels.—In 26 the bowel movements were "regular"; in 12, "sluggish"; and in 92 (65 per cent.), "constipated." In 10 there was diarrhea.

Character of Complaint.—One hundred and four (74.2 per cent.) gave histories of discomfort intermittently ("attacks," "spells," etc.). In 36 (26.6 per cent.) instances the ailment was continuous. In many cases there was an early history of "attacks," with recent change to continuous discomfort, frequently associated with loss of weight and strength. The "attacks" were variously stated as three to five years; two to three years; or two to six months, or two to five weeks apart. They were often noted as lasting a few hours or days to two to six months, irrespective of medical or other treatment. The attacks frequently bore relation to the seasons—spring and fall being favorites.

Previous Disorders of "Digestion."—Eighty-one per cent. of the cases came with a diagnosis, frequently self-given, of "dyspepsia" or "indigestion," usually "chronic." Table III furnishes significant and etiologic information—and not altogether useless diagnostically—respecting this class of cases.

TABLE III.—DURATION OF SYMPTOMS

Years	No. of Cases	Per Cent.
Less than 1	8	5.7
1- 5	30	21.4
5–10	32	22.8
10–15	29	20.7
15–20	14	10.0
20–25	9	6.4
25–30	7	5.0
Over 30	11	7.8

The table makes apparent that nearly 54 per cent. of the patients had been affected with disorders of "digestion" for from five to twenty years before operation; about 21 per cent. had been ill less than five years.

Age has only relative importance in the estimation of duration of an ulcerative process in the stomach. Frequently patients in the sixth decad of life have been perfectly well to within a few months of the disability that finally leads to operation (*e. g.*, six months, age fifty-eight years; five months, age fifty-three years; three months, age fifty-three years; etc.), while young adults give a history of from ten to twenty years of "indigestion."

Symptomatology.—*1. Pain.*—Of the 140 proved ulcers without food retention in the series, pain is the one constant complaint.

(*a*) *Character of Abdominal Discomfort.*—This was styled "distress" in 17; "burning feeling" in 21; "gnawing" in 25; "dull ache" in 33; severe ache in 13. In 31 there was history of colicky attacks ("cramps," "doubling up," "tearing," etc.). In 18 instances (12.7 per cent.) these were severe enough to require hypodermatic administrations of opiates. In 64 instances (45.7 per cent.) there were sensations of "upward pressure." In 17 (12.2 per cent.) pain or distress was continuous or appeared irregularly. In 27 instances (19.2 per cent.) night pain was a distressing feature.

(*b*) *Location, Symptomatically, of Abdominal Discomfort.*—In 112 cases (80 per cent.) discomfort was said to be epigastric; in 29, epigastric to the rib edges (more often to the right); in 18 in the "pit of the stomach"; in 8 in the abdomen generally; in 2 in the "small of the back."

(*c*) *Transmission of Pain.*—In 52 instances (37.1 per cent.) no transmission was given. In 25 cases pain was referred to the back (right side, 22; left, 3), usually below the tip of the scapula; in 25 cases to the rib edges (right, 20; left, 5); in 10 to the lower esophagus; in 7, the infranavel region; in 7 to the shoulder-blades (right, 5; left, 2); in 3 each to navel, nipples, thorax generally, and "tip" of sternum, and in 2 to the throat.

(*d*) *Food Relation.*—In 123 cases (87.8 per cent.) pain had a definite relation to ingestion of food. The summary in Table IV demonstrates the actual time relation of food and abdominal discomfort.

TABLE IV

Time of Pain in Hours After Eating	No. of Cases	Percentage
Immediately	4	2.8 per cent.
Less than 1 hour	17	12.2 "
1–2 hours	22	15.7 "
2–3 hours	33	23.7 "
3–4 hours	34	24.7 "
4–5 hours	10	7.1 "
Over 5 hours and irregularly	20	14.2 "

Some overlapping is exhibited, inasmuch as pain may vary as to time in different attacks. It will be noted that in more than

79 per cent. of instances pain appeared within four hours following the ingestion of food. The taking of food frequently temporarily relieved actual pain, as shown below.

TABLE V

Location of Ulcers	Time (Hours); Cases (Number)								
	Less than 1	1–2	2–3	3–4	4–5	Over 5	Irregularly	Total	Night Pain
Pyloric............	6	5	23	19	6	0	6	65 (46.4 per cent.)	12
Prepyloric..........	0	1	1	2	1	0	0	5 (3.5 per cent.)	0
Lesser curvature...	5	10	13	7	3	1	4	43 (30.7 per cent.)	14
Near cardia.........	4	2	1	2	0	0	0	9 (6.4 per cent.)	0
Posterior wall......	4	2	2	2	1	0	1	12 (8.5 per cent.)	1
Anterior wall.......	0	0	1	1	0	0	0	2 (1.4 per cent.)	0
Total..........	19	20	41	33	11	1	11	136	27

Unclassified, 4.
Night pain cases not included in totals.

(*e*) *Relation of Time to Pain or Distress to Location of Ulcer.*—Table V demonstrates that, irrespective of location of ulcer, 83 per cent. have pain or distress within four hours after taking food, and more than 54 per cent. have pain or distress within two or four hours after eating. More than 64 per cent. of ulcers involving the pylorus have pain from two to four hours after eating; more than 53 per cent. of lesser curvature ulcers have pain from one to three hours after eating; more than 66 per cent. of ulcers near the cardia have pain less than two hours after eating, and more than 44 per cent. less than one hour after eating; more than 66 per cent. of ulcers on the posterior wall have pain within three hours after eating, and 33 per cent. have pain within one hour after eating.

(*f*) *Pain Control.*—Except in acute attacks (*e. g.*,"colics,"perforation, etc.), gastric ulcer pain is usually eased or relieved by limitation of the amount and character of ingested food (diet), the taking of food when distress is marked (food-ease), the neutralization of acid by the alkalis or by emptying the stomach (vomiting or lavage); as has been shown in this series, opiates were required in 12.7 per cent. of instances, usually in aggravated "spells."

Table VI demonstrates the relative value in our series of the various common pain controls. The tabulations may be so read as to show the relative frequency of relief from any combination of pain controls. The most common combination of controls proved to be diet, food ingestion, alkali, and vomiting.

TABLE VI.—PAIN CONTROL

Type of Control	Total Cases	Food	Vomiting	Liquids	Alkali	Lavage	Diet	Rest	Pressure	Opiate
Food	93	0	49	14	68	14	83	15	5	11
Vomiting	71	49	0	9	41	11	65	10	2	7
Liquids	16	14	9	0	13	4	14	1	2	0
Alkali	82	68	41	13	0	9	77	9	3	10
Lavage	15	14	11	4	9	0	12	1	0	0
Diet	121	83	10	1	9	1	0	12	1	13
Rest	20	15	10	1	9	1	12	0	1	3
Pressure	7	5	2	2	3	0	4	1	0	1
Opiate	18	11	7	0	10	0	13	3	1	0

Explanation.—Read times each control gave distress relief in column "Total Cases." For combinations of pain controls read table up and down.

Table VII attempts to correlate these factors with respect to the locations of the ulcer demonstrated operatively.

(*g*) *Relation of Position of Ulcer to Pain Control.*—

TABLE VII.—RELATION OF POSITION OF ULCER TO PAIN CONTROL

	Diet	Food Relief	Alkali	Vomit
Pyloric	57	49	37	36
Prepyloric	0	0	0	0
Lesser curvature	51	37	38	26
Near cardia	3	2	1	2
Posterior wall	7	5	4	3
Anterior wall	4	3	3	1
	132	96	83	68

(*h*) *Areas of Abdominal Tenderness by Palpation.*—Of the 140 proved ulcer cases, 126 (95 per cent.) exhibited epigastric tenderness. In 109 (77.8 per cent.) the tenderness was more marked to the right of the midline. In 17 (12 per cent.) the tenderness was prominent to the left of the midline. In 23 instances (16+ per cent.) there was especial tenderness in the "pit," irrespective of general epigastric sensitiveness. In 20 instances (14+ per cent.) there was definite exaggeration of tenderness at the right rib border, distinct from wide-spread epigastric muscle spasm. Five patients (3+ per cent.) exhibited especial left rib margin tenderness. In 5 cases (3 + per cent.) the area just above the navel was most painful to pressure. On but one patient was no abdominal tenderness demonstrated. Ridges, invariably tender, were palpable 4 times.

(*i*) *Relation of Areas of Abdominal Tenderness to Location of Ulcer as Found at Operation.*—Table V shows that, of the 140 ulcers examined, practically half (49.9 per cent.) were pyloric or prepyloric, while more than four-fifths (80.6 per cent.) of the entire series were located at the pylorus and the pyloric half of the lesser curvature.

It has been shown above that in 95 per cent. of our cases here reported there was definite epigastric tenderness. While 46.4 per cent. of all the ulcers were located at the pylorus, in only 14+ per cent. was there increased tenderness toward the right rib margin—*i. e.*, the anatomic situation of the pylorus. While 30.7 per cent. of all the ulcers were on the lesser curvature, but 16 + per cent. of the cases showed definite tenderness in the pit, or midepigastrium.

We have also shown that, symptomatically, the patients' complaints of distress are in close harmony with the physical evidences of tenderness, In this classification 80 per cent. referred the pain to the epigastrium generally, 14 per cent. to the right costal arch region, and 12.8 per cent. to the pit. There were 8 (5.75 per cent.) ulcers located at or near the cardia. In more than twice that number there was noted high pit tenderness.

It would seem that, only when taken with other observations, are pain areas, symptomatically, or points of abdominal tenderness of value in definitely localizing ulceration of the stomach.

(*j*) *Relation of Evidences of Perforation of Gastric Ulcer to Actual Evidences of Such as Demonstrated at Operation.*—In our series 46 cases (32.8 per cent.) had histories and physical findings of acute or chronic perforation. In 24 cases (17 + per cent.) suggestion of perforation was possible. At operation 51 (36.4 per cent.) ulcers had perforated (9 acute, 3 subacute, 39 chronic). It would seem that only when history and physical findings of perforation are quite marked can one safely prognosticate an operative finding with a fair degree of certainty.

2. Vomiting.—*(a) Frequency.*—This proved a prominent symptom. Of the 140 cases considered, 99 (70.7 per cent.) gave history of at some time vomiting sour fluid, food, or blood. Of the 99 cases, 65 vomited some fluid blood alone; 24 vomited sour fluid and food. In the series 50 cases vomited but had no hematemesis; 31 vomited and also had hematemesis; 18 had hematemesis alone. Ten cases regularly *induced* vomiting of sour fluid and food to gain relief from pain.

Of the 99 who vomited, 39 vomited regularly. Eleven had "spells" with vomit-free intervals of greater or less length, while 49 vomited only occasionally.

Nausea, Waterbrash, Eructations.—In 9 cases nausea without vomiting was a distressing symptom. "Waterbrash," with or without vomiting, was prominent in 26 instances (19+ per cent.).

Pyrosis and eructations were noted in 123 (87.8 per cent.).

(b) Time of Vomiting.—Of the 99 who vomited, in 35 (35.3 per cent.) the vomiting occurred when abdominal distress was most marked. In 28 instances (28 per cent.) ingestion of food precipitated vomiting. Twenty-nine (29+ per cent.) vomited irregularly. In 7 (7 per cent.) night vomiting was prominent.

(c) Food Ingestion Vomiting.—Table VIII summarizes this class of cases. It will be noted therein that more than 53 per cent. of these cases vomit within three hours following the taking of food:

TABLE VIII.—FOOD INGESTION—VOMITING

TIME	NUMBER
Less than 1 hour after eating	6
1–2 hours after eating	4
2–3 " " "	5
3–4 " " "	6
4–5 " " "	3
Over 5 " " "	4

(*d*) *Relation of the Position of the Ulcer to Vomiting.*—In Table IX we have summarized our experience in this respect with regard to character of vomitus and location of ulcer. The most marked feature of the table is the numeric evidence supporting the clinical experience that ulcers at the pylorus and pyloric half of the lesser curvature are commonly associated with vomiting. This appears so especially when we recall that this series deals with gastric ulcer where the emptying power of the stomach has not been interfered with.

TABLE IX.—RELATION OF VOMITING TO LOCATION OF ULCER FOUND AT OPERATION

Location	Blood Alone	Sour and Food without Hematemesis	Hematemesis and Sour and Food	Food
Pyloric	10	23	17	9
Prepyloric	0	0	1	1
Lesser curvature	8	21	8	11
Near cardia	0	2	2	0
Posterior wall	0	3	2	2
Anterior wall	0	1	1	1
Totals	18	50	31	24

3. Hemorrhage.—(*a*) *Frequency.*—While clinically this sign has especial emphasis placed upon it, of the 140 proved gastric ulcers analyzed herewith, but 57 (40.7 per cent.) gave a history of bleeding. Of this number 47 (33.7 per cent.) had hematemesis, with or without melena; 25 had hematemesis alone; 32 (22.8 per cent.) had melena, with or without hematemesis; 10 (7.1 per cent.) had melena alone; 22 (15 + per cent.) had both hematemesis and melena.

Number.—The minimum number of hemorrhages was 1, the maximum, 10.

(*b*) *Severity of Hemorrhage.*—In 13 instances the patient experienced no particular inconvenience; in 21 there was faintness, while 23 patients actually fainted.

Amount of Blood Lost.—This was given as varying from a "half-pint" to "a gallon."

(*c*) *Character of Hematemesis.*—In 2 instances large clots were vomited. In the remaining cases the blood was fluid.

(*d*) *Relation of Location of Ulcer to Hemorrhage.*—Our experience is represented in Table X. It may be observed that, irrespective of location of the ulcer, hematemesis alone is most common. It is also interesting to observe that melena may accompany ulcer located anywhere in the stomach-wall, and that in a considerable proportion of cases this may occur without hematemesis.

TABLE X.—RELATION OF POSITION OF ULCER TO HEMORRHAGE

Location	Hematemesis Alone	Hematemesis and Melena	Melena Alone	Total Hemorrhage Each Location
Pyloric	10	12	4	26
Prepyloric	1	2	0	3
Lesser curvature	9	4	4	17
Near cardia	2	3	0	5
Posterior wall	3	1	1	5
Anterior wall	0	0	1	1
Totals	25	22	10	57

(*e*) *Relation of Hemorrhage to the Character of Ulcer Operatively Demonstrated.*—Table XI details our findings. It is apparent that while all classes of ulcer bleed, yet nearly two-thirds (63+ per cent.) of those doing so show some grade of perforation at the laparotomy.

TABLE XI.—RELATION OF HEMORRHAGE TO CHARACTER OF ULCER FOUND AT OPERATION

Character of Ulcer	No. of Cases
1. Indurated ("calloused") ulcer	16
2. Acute perforating ulcer	6
3. Chronic perforating ulcer	8
4. Chronic indurated perforating ulcer with adhesions	17
5. Saddle ulcer	5
6. Saddle ulcer with adhesions	5
Total	57

4. Test-meal Findings.—In the series of gastric ulcers operated on in the Mayo Clinic (404 cases) before mentioned, it will be recalled that 264 (65.3 per cent.) of these showed definite food retention by the tests of Strauss and Hansmann. In the remaining 140 cases which comprise this analysis 131 (93.7 per cent.) routine test-meal reports are available to tabulation. In 9 instances test-meals were not given, or if given, only absence of food retention is noted.

(*a*) *Blood.*—This was noted in 16 (12.2 per cent.) macroscopically or chemically by guaiac or benzidin tests.

(*b*) *Bile.*—Twelve (9.2 per cent.) gastric extracts showed bile macroscopically or by chemic test (Goodel).

(*c*) *Lactic acid* was demonstrated four times (3.1 per cent.) by the modified Uffelmann test.

(*d*) *Quantitative Estimation of Inorganic Acid.*—The figures quoted are those obtained from filtered gastric extracts obtained about one hour following the Ewald breakfast, which had been preceded twelve hours by a full meal, including boiled rice and raisins.

Inasmuch as pyloric obstruction with food retention masks the true secretory picture in gastric ulcer, the tables compiled from our cases would appear to be especially suggestive.

Table XII details the quantitative estimation of total acidity and free hydrochloric acid by the Töpfer method.

TABLE XII.—TEST-MEAL ACIDITIES

	0	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	OVER 100
Total acidity	0	4	2	5	16	24	29	25	13	4	5	4
Free HCl	5	2	5	23	26	27	18	12	6	5	0	2
Totals	5	6	7	28	42	51	47	37	19	9	5	6

Table XIII summarizes the amounts of "combined" hydrochloric acid.

TABLE XIII.—COMBINED HCl

	0	0–10	10–20	20–30	30–40	40–50
Combined HCl...........	4	26	83	17	1	0

Total Acidity.—In 79.1 per cent. of the cases this ranged between 35 and 75, with an average of 55.

Free HCl.—More than 79 per cent. of meals showed free HCl of from 25 to 55, with an average of 42.5, irrespective of location of ulcer (*vide infra*).

"*Combined*" *HCl.*—In more than 82 per cent. of instances this varied between 10 and 20. Only four times was "combined" HCl absent.

(*e*) *Relation of Total Acidity and Free HCl to Location of Ulcer Demonstrated Operatively.*—The summary to Table XIV demonstrates that total acidity is quite noticeably higher in ulcers involving the lesser curvature than in those of any other location except on the anterior wall. The 2 cases tabulated in the latter position showed an average total acidity of 70. It would seem that this number is too small on which to base conclusions.

TABLE XIV.—RELATIONS OF TOTAL ACIDITY TO LOCATION OF ULCER FOUND AT OPERATION

Location	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	Over 100	Total
Pyloric	0	1	0	9	11	11	15	8	4	3	1	63
Prepyloric	1	0	1	1	1	1	0	0	0	0	0	5
Lesser curvature	2	1	3	4	4	5	10	8	2	0	3	42
Near cardia	0	0	1	0	2	3	2	0	0	0	0	8
Posterior wall	1	0	0	0	4	4	2	0	0	0	0	11
Anterior wall	0	0	0	0	0	1	0	0	1	0	0	2
Totals	4	2	5	14	22	25	29	16	7	3	4	131

Summary

Average total acidity in pyloric ulcer	56.0
" " " " lesser curvature, ulcer	62.4
" " " " ulcer at or near cardia	51.0
" " " " ulcer posterior wall	48.7
" " " " ulcer anterior wall	70.0

Table XV makes apparent that our material showed noticeably greater free HCl in ulcers at the pylorus than in any other class, except the 2 tabulated as being on the anterior wall. It will be noted that this is the reverse of the figures returned by a consideration of the total acidity above.

TABLE XV.—RELATION OF FREE HCl TO LOCATION OF ULCER FOUND AT OPERATION

Location	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	Over 100	Total
Pyloric	2	2	7	10	13	11	6	5	5	0	2	63
Prepyloric	1	2	0	0	1	0	1	0	0	0	0	5
Lesser curvature	3	1	9	7	12	7	2	1	0	0	0	42
Near cardia	0	0	2	4	2	0	0	0	0	0	0	8
Posterior wall	1	0	3	3	2	0	2	0	0	0	0	11
Anterior wall	0	0	1	0	0	0	1	0	0	0	0	2
Totals	7	5	22	24	30	18	12	6	5	0	2	131

SUMMARY

Average free HCl in pyloric ulcers	46.5
“ “ “ “ lesser curvature ulcers	38.8
“ “ “ “ ulcers at or near cardia	35.0
“ “ “ “ ulcers on posterior wall	36.8
“ “ “ “ ulcers on anterior wall	45.0

Both tables demonstrate that location of ulcer plays a relatively small part as a local "irritative" factor in the production of acidity. The figures returned also show that while high total acidity and free HCl are occasionally met with in gastric ulcer of the class under consideration, they are the exception rather than the rule.

TABLE XVI.—RELATION OF COMBINED ACIDITY TO LOCATION OF ULCER FOUND AT OPERATION

Location	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	Over 100	Total
Pyloric	12	45	5	1	..	..	..	..	..	..	..	63
Prepyloric	1	3	1	0	..	..	..	..	..	..	..	5
Lesser curvature	13	25	4	0	..	..	..	..	..	..	..	42
Near cardia	0	7	1	0	..	..	..	..	..	..	..	8
Posterior wall	3	3	5	0	..	..	..	..	..	..	..	11
Anterior wall	1	0	1	0	..	..	..	..	..	..	..	2

SUMMARY

Average combined acidity in ulcer at pylorus	14.2
“ “ “ “ ulcer of lesser curvature	12.8
“ “ “ “ ulcer at or near cardia	12.5
“ “ “ “ ulcer on posterior wall	16.8
“ “ “ “ ulcer on anterior wall	15.0

(*f*) *Combined Hydrochloric Acid.*—Table XVI makes evident that in food retention, free gastric extracts combined hydrochloric acid can be almost constantly demonstrated. There is relatively little difference between the amounts where ulcers are variously located. Our series showed a slightly lower average when ulcers were at the cardia than when such were at the pylorus or on either wall of the stomach.

(*g*) *Relation of Free HCl Content to Age of Patient.*—Table XVII details the results returned by this study. It will be seen that while the highest average acidity is shown in the group of ulcers occurring in the third decad, quite comparable averages are returned by analyses in patients in the sixth and the eighth decads. In no decad are the averages very low.

TABLE XVII.—RELATION OF ACIDITY TO AGE OF PATIENT

Age	Acidity—Per Cent											
	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	Over 100	Total with Meal
(0) 0–10......	0	0	0	0	0	0	0	0	0	0	0	0
(0) 10–20.....	0	0	0	0	0	0	0	0	0	0	0	0
(21) 20–30.....	1	0	1	4	6	4	3	0	0	0	2	21
(38) 30–40.....	2	2	8	7	6	4	4	1	2	0	0	36
(31) 40–50.....	4	1	5	6	6	2	1	1	3	0	0	29
(39) 50–60.....	0	2	7	6	7	6	4	4	0	0	0	36
(8) 60–70.....	0	0	2	2	1	1	0	0	0	0	0	6
(3) Over 70...	0	0	0	1	1	1	0	0	0	0	0	3
Totals....	7	5	23	26	27	18	12	6	5	0	2	131

Summary of Table XVII

Average free HCl—age 20–30	48.2
“ “ “ “ 30–40	41.1
“ “ “ “ 40–50	39.3
“ “ “ “ 50–60	45.0
“ “ “ “ 60–70	36.6
“ “ “ “ Over 70	45.0
Average free HCl for all ages	42.5+

(*h*) *Relation of Free HCl Acidity to Time of Pain.*—The information returned by Table XVIII is suggestive. It is apparent that, following food ingestion, a progressively increasing number of cases show pain manifestations up to the fourth hour. Between the third and fourth hours the greatest number complained of distress. The summary of average acidities shows that the degree of acidity increases up to the fourth hour after eating. It would seem that this series furnishes instructive data respecting relation between distress and concentration (?) of free HCl. After the fourth hour there is a progressive diminution in acidity, and a correspondingly smaller number of cases manifest pain in these periods.

When continuous distress is complained of, the average acidity does not appear to be as high as when definite periods of pain following food ingestion are evidenced.

TABLE XVIII.—RELATION OF FREE HCl ACIDITY TO TIME OF PAIN

TIME AND GROUP	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	OVER 100	TOTAL
Immediately after eating	1	0	0	1	1	1	0	0	0	0	0	4
Less than 1 hour after eating	2	0	2	5	2	1	3	1	0	0	0	16
Less than ½ " " "	1	1	2	5	5	3	2	0	0	0	0	19
2–3 hours after eating	0	0	9	7	3	4	5	2	2	0	0	32
3–4 " " "	0	2	3	2	12	5	1	1	2	0	2	30
4–5 " " "	0	0	3	2	2	2	0	1	1	0	0	11
Over 5 hours after eating	0	0	2	0	1	0	0	1	0	0	0	4
Irregular	2	1	2	3	1	0	1	0	0	0	0	10
Continuously	1	1	0	1	0	2	0	0	0	0	0	5

SUMMARY

Group 1—Average free HCl	36.6
Group 2— " " "	40.3
Group 3— " " "	40.3
Group 4— " " "	46.0
Group 5— " " "	51.3
Group 6— " " "	46.0
Group 7— " " "	42.5
Group 8— " " "	29.0
Group 9— " " "	33.0

Relation of Free HCl to Vomiting.—Table XIX shows that more than 60 per cent. of all cases that vomited had free HCl between 20 to 50. The average was 35.1.

TABLE XIX.—RELATION OF ACIDITY TO VOMITING (FREE HCl)

Group	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	Over 100	Total
Vomited	3	4	20	20	20	12	10	3	5	0	2	99
No vomit	3	1	3	6	6	6	2	4	1	0	0	32

Of the non-vomiting class, but 46 per cent. are grouped between acidity 20 to 50. Their average free HCl was 37+.

More than 56 per cent. of the cases giving no history of vomiting had free HCl between 40 to 80. The average in this group was 57.

(*i*) *Relation of Free HCl to Hemorrhage.*—Table XX demonstrates that 57 per cent. of ulcers evidencing *hematemesis* had acidity between 20 to 50. The average acidity was 35+.

TABLE XX.—RELATION OF ACIDITY TO HEMORRHAGE

Group	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	Over 100	Total
Hematemesis	2	1	6	14	6	5	5	3	2	0	2	46
No hemorrhage	5	2	13	11	17	14	6	2	3	0	0	73
Melena	0	1	2	1	3	1	1	1	0	0	0	10

More than 57 per cent. of cases giving no history of hemorrhage had acidity between 30 to 60. The average acidity was 46.

Melena.—Sixty per cent. of cases had acidity between 20 to 50. The average acidity was 36+.

(*j*) *Relation of Free HCl Acidity to Character of Ulcer.*—Reference to Table XXI demonstrates that the highest acidities are associated with perforated ulcers. The highest average acidity is shown to be associated with subacute perforating ulcer.

TABLE XXI.—RELATION OF FREE HCl ACIDITY TO CHARACTER OF ULCER

GROUP	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	OVER 100	TOTAL
Subacute perforation	0	0	1	0	1	2	2	1	1	0	1	9
Chronic perforating	1	1	1	3	2	4	0	0	0	0	0	12
Chronic perforation with adhesions	0	1	5	9	5	2	3	3	1	0	1	30
Indurated calloused	6	1	11	13	15	8	7	1	4	0	0	66
Saddle	0	1	3	1	2	2	2	1	0	0	0	12
Saddle with adhesions	0	0	1	1	0	0	0	0	0	0	0	2

SUMMARY

Subacute perforation, average acidity	64.1
Chronic perforation, " "	39.1
Chronic perforation with adhesions, average acidity	46.6
Indurated calloused, average acidity	42.1
Saddle, " "	43.3
Saddle with adhesions, " "	30.0

(*k*) *Relation of Free HCl Acidity to Nausea.*—In 12 instances nausea was a distressing feature. Half of this number had free HCl between 20 to 50. The average acidity of this class was 36.6. The average acidity of the entire group was 49.5.

(*l*) *Relation of Free HCl Acidity to Pyrosis.*—In 22 instances pyrosis was a prominent symptom. More than 67 per cent. had acidity between 30 to 70. The average acidity of this class was 47+.

TABLE XXII.—RELATION OF FREE HCl ACIDITY TO NAUSEA

GROUP	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	OVER 100	TOTAL
Nausea	1	1	2	1	3	0	1	1	1	0	1	12
No nausea	6	4	21	25	24	18	11	5	4	0	1	128

TABLE XXIII.—RELATION OF FREE HCl ACIDITY TO PYROSIS

GROUP	0–10	10–20	20–30	30–40	40–50	50–60	60–70	70–80	80–90	90–100	OVER 100	TOTAL
Pyrosis	0	0	2	5	4	3	3	1	2	0	0	22
No pyrosis	7	5	21	21	23	15	9	5	3	0	0	118

Operative Findings.—*Location.*—Table V demonstrates the number of ulcers in each situation as found at laparotomy. It will be noted that the pylorus proper was involved in 65 instances (46.4 per cent.), while in 75 cases (53.6 per cent.) the ulcer was in other portions of the stomach-wall. Two instances revealed 2 ulcers each.

Character of Lesion.—The tabulations already made (Tables XI and XXI) show in detail the number of each class of ulcer found on laparotomy. In addition to this general clinical classification, we may state that of the 50 ulcers which were available for microscopic examination, 12 (24 per cent.) were noted as active "inflammatory," and 6 (12 per cent.) showed beginning carcinoma. The remaining 32 were indurated or "calloused" ulcers. In 5 cases an existing or suspected lues was an etiologic and prognostic factor.

Extragastric Lesions Demonstrated by Laparotomy.—*Appendix.*—In 49 instances (35 per cent.) sufficiently marked evidences of disease were found in the appendix to warrant its removal. It has already been stated above that 8.5 per cent. of the cases in this series had had appendicectomy before coming to the clinic. The combined figure, 43.5 per cent., indicates that more than two-fifths of all patients of this group had appendix alterations. The observation is sufficiently striking to warrant emphasis from at least three points: (1) The etiologic relation between appendix alterations and coincident or subsequent changes in the stomach-wall; (2) the prognostic limitations respecting normal gastro-intestinal function following appendicectomy; (3) the advisability of careful anamnesis and upper abdominal examination of individuals whose only ailment, symptomatically, appears to be located in the right lower quadrant.

Gall-bladder.—Operatively, cholecystitis and cholelithiasis were demonstrated in 21 (15 per cent.) individuals. Previous to entering the clinic 7.8 per cent. of the patients in this series had already had operations for gall-stones or cholecystitis. The combined statistics indicate that 22.8 per cent. had alterations in the gall-tract apart from gastric pathology. Combining the figures from observations upon the appendix and gall-bladder, it is seen that nearly two-thirds (66.2 per cent.) of the cases in this report had associated with definitely proved gastric disease anomalies of these divisions of the digestive mechanism. In addition to the above, Lane kink was found twice, carcinoma of the gall-tract once, and pancreatitis 4 times (2.8 per cent.).

Operative Procedures.—Table XXIV offers significant information respecting operative versatility required to meet the particular anomaly in the given subject in order to secure maximum results:

TABLE XXIV

Operation	Number of Cases
Posterior gastro-enterostomy (Mayo)	49
Gastro-enterostomy and excision	14
Gastro-enterostomy and sutures	24
Excision alone	24
Compression sutures	5
Anterior gastro-enterostomy	4
Pylorectomy or resection, without or with gastro-enterostomy	4
Finney	3
Finney and sutures	1
Heineke-Mikulicz, without or with gastro-enterostomy	4
Billroth No. 2 and posterior gastro-enterostomy, without or with excision	3
Infolding of ulcer	3
Jejunostomy and Witzel	1
Unclassified (plastic)	1
Total	140

In view of Cannon's recent work upon gastric peristalsis, it would appear that choice of operative procedure to fit the case in hand is quite as essential as is the recommending of patients to submit to laparotomy.

In this series 2 (1.4 per cent.) cases died within a month following operation. One case had chronic perforating ulcer with adhesions that developed obstruction, following extensive excision. The other case was one of large perforating posterior wall with adhesions involving the pancreas.

The records show that another patient died five months following excision of a perforating anterior wall ulcer, while two years following excision of a posterior wall ulcer a fourth patient succumbed to general sarcomatosis (primary in the pancreas). To July 1, 1912, no other deaths had been reported.

Secondary Operations.—Six cases required second operation within one and one-half years following the primary laparotomy. The conditions were as summarized in Table XXV. With the exception of the case later developing a duodenal ulcer, the ulcers requiring the second operation were rather unusual as to either character or situation.

TABLE XXV

Primary Operative Finding	Primary Operative Procedure	Secondary Operations
1. Ulcer posterior wall and hour-glass stomach.....	Billroth No. 1 and excision	Posterior gastro-enterostomy for obstruction
2. Large calloused ulcer at pylorus.............	Infolded	Posterior gastro-enterostomy
3. Ulcer at pylorus with marked adhesions......	Finney	Posterior gastro-enterostomy
4. Ulcer at pylorus with subacute perforation to head of pancreas.......	Excision	Posterior gastro-enterostomy
5. Ulcer at base of anterior wall	Posterior gastro-enterostomy	Duodenal ulcer, excision, plastic
6. High perforating ulcer on lesser curvature.....	Excision	Posterior gastro-enterostomy

Summary

The above clinical analysis of 140 cases of operatively demonstrated surgical gastric ulcer without food retention appears to warrant the following statements:

1. In more than one-third of operatively demonstrated gastric ulcers the stomach's emptying power is maintained.

2. Ninety-two per cent. of this group of ulcers occurs between the ages of thirty and sixty. Males are affected three times as frequently as females. The American-born farmer furnishes a large majority of gastric ulcers.

3. Irregularity of food ingestion with the use of alcoholic stimulants is not an uncommon concomitant of gastric ulcer.

4. A rather striking frequency of history of previous infectious disease is shown—18.9 per cent. of our cases had had typhoid fever.

5. A mild grade of secondary anemia is present in the average gastric ulcer.

6. Weight loss averaging more than 20 pounds, without marked cachexia, was shown in this series. The loss may be so rapid as frequently to suggest malignant disease. Some cases consistently gain weight.

7. Appetite is lost or is capricious in nearly three-fourths of the cases. More than 65 per cent. are constipated.

8. Nearly three-fourths of the cases have "spells" or "attacks" of discomfort, with good health between such. Such a history may extend over thirty years, without alarming clinical manifestations. The attacks are usually called "biliousness" or "dyspepsia." They often show a peculiar seasonal relation.

In 36 per cent. of instances the disability is continuous, with or without nutritional disturbances.

9. Abdominal pain or distress is a constant symptom in gastric ulcer. It is "colicky" in nature in more than 22 per cent. of cases, requiring hypodermatic medication in 12.7 per cent. It is frequently mistaken for appendiceal or gall-bladder disease, and is often associated with such in addition to gastric ulcer. Night pain, with interference with sleep, is present in 19.2 per cent. of cases. Eighty per cent. of patients complain of epigastric distress, frequently referred to the right rib margin or the back.

In 87.8 per cent. of proved ulcers pain or distress has definite relation to food ingestion. Eighty-three per cent. of cases show pain or distress coming on within four hours following eating. Nearly two-thirds of pyloric ulcer cases have discomfort from two to four hours after eating; more than one-half of lesser curvature ulcers, from one to three hours after eating; more than two-thirds of posterior wall ulcers within three hours after eating, and more than two-thirds of ulcers near the cardia less than two hours after eating, with more than 44 per cent. of this class less than one hour after eating.

Discomfort is most frequently controlled by ingestion of food, alkalis, and vomiting. Opiates were required by 12.2 per cent.

On palpation, epigastric tenderness is exhibited in 95 per cent.

of cases. In more than three-fourths of our series tenderness was most marked in the right upper abdominal quadrant. Palpable ridges were present in 2.8 per cent. of cases.

More than four-fifths of the ulcers were located at the pyloric half of the stomach, and this was in general the anatomic area of greatest complaint or distress on examination.

The diagnosis of the character of ulcer to be found on exploration is possible only where a careful anamnesis is made.

10. Vomiting is present in nearly three-fourths of gastric ulcers without anatomic pyloric stenosis. About 17 per cent. vomit food. Only rarely is delayed vomiting observed. Vomiting is induced in more than 10 per cent. of cases to relieve pain. Nearly 40 per cent. of patients vomit regularly. "Waterbrash" is a prominent feature in 19 per cent.; pyrosis and eructations, in 87.8 per cent. In nearly one-third of the cases vomiting comes at the time of maximum abdominal distress. In 28 per cent. the ingestion of food precipitated vomiting; more than 53 per cent. vomit within three hours after eating. In 7 per cent. night vomiting is a feature. Ulcers at the pyloric half of the stomach are most commonly associated with vomiting, even when there is no interference with the emptying power of the stomach.

11. *Hemorrhage.*—Of 140 proved ulcers in this group, bleeding (hematemesis or melena) was noted in but 40.7 per cent. About one-fourth of the cases had hematemesis alone; one-third hematemesis with or without melena, while 7.1 per cent. had melena alone.

Severe hemorrhage or frequently repeated moderate hemorrhages are usually associated with faint feelings or actual fainting (40+ per cent.).

Hematemesis is more frequent than melena, but melena alone may occur entirely independent of the location of the ulcer. While bleeding is associated with any type of ulcer, nearly two-thirds of those doing so show operative evidences of perforation.

12. *Test-meal Findings.*—*Acidity.*—Irrespective of location of the ulcers, the average total acidity was 55; the average HCl, 42.5; the "combined" HCl, in 82 per cent. of cases, between 10 to 20. Total acidity is most commonly higher in ulcers involving

the lesser curvature and anterior wall than when other parts of the stomach are affected. High free HCl is noticeably more frequent when the ulcer is at the pylorus. While high free HCl is usual in cases in the third decad of life, this is not the rule.

Following food ingestion, the great majority of cases show pain within four hours. This series shows that during this period free HCl is progressively increasing. Patients complaining of continuous distress do not necessarily have high acidity.

Vomiting is not usually associated with high free HCl. More than half of the non-vomiting cases had higher acidity than was the average of those vomiting. The average free HCl of patients bleeding was 35 +. More than half of the cases giving no history of hemorrhage had average free HCl of 46.

The highest free HCl averages are associated with subacute perforating ulcer.

13. *Operative Findings.*—More than two-fifths of the ulcers were at the pylorus.

Of 50 ulcers microscopically examined in this series, 24 per cent. showed inflammatory change, 12 per cent. beginning carcinoma.

In 35 per cent. of instances diseased appendix was associated with gastric ulcer. In 15 per cent. cholecystitis and cholelithiasis were demonstrated as concomitant processes. In nearly two-thirds of this group of gastric ulcer diseased appendix and gall-bladder were revealed operatively. In view of these figures it is evident that all laparotomies should be thoroughly exploratory, even when a well-marked gastric ulcer has been demonstrated.

Operative procedure should be adapted to the individual finding on exploration. A routine technic is frequently accountable for poor post-operative progress.

Prompt relief of symptoms with a comfortable after-course is the rule following operative treatment of retention free ulcer cases.

This series shows an operative mortality of 1.4 per cent. Rather more than 4 per cent. required a second operation. These were generally ulcers of unusual type.

INVOLVEMENT OF REGIONAL LYMPHATIC GLANDS IN CARCINOMA OF THE STOMACH*

FROM A STUDY OF 200 RESECTED SPECIMENS

WILLIAM CARPENTER MACCARTY

ASSISTED BY

JOHN MINOR BLACKFORD

A historic review of gastric therapeutics should give the surgeon credit for having demonstrated that all palpable tumors of the stomach are not inoperable, a fact learned from experience in palliative surgery, especially in cases in which the surgeon tried to save the patient from starvation by resection or gastro-enterostomy. Patients with extensive lesions in the stomach often lived comfortably over a period of several years. This was far beyond the expectations of the surgeon.

Such clinical and operative experience and the close association of carcinoma with gastric ulcer—which has been demonstrated by the surgical pathologist—have led conservative but progressive surgeons to explore, in doubtful cases, rather than to guess about the abdominal contents. Many cases which were considered clinically "inoperable" have been found to be operable; many carcinomatous stomachs have been diagnosed clinically simple gastric or duodenal ulcers; many "gastric ulcers" have been found to be ulcers of the duodenum; and many lesions in the gall-bladder, duodenum, and appendix have been mistaken for gastric ulcers.

Recognition of the operability of cases which a few years ago were considered inoperable has been a great step forward in the art and science of operative gastric therapeutics. Some patients have been completely cured of gastric disturbances, many relieved for a period of years, and others saved from a death of starvation.

---

* Reprinted from "Annals of Surgery," June, 1912, pp. 811–843.

Good results have been doubtless due in part to irregularity in the rapidity of lymphatic involvement—a condition in gastric carcinoma which has occupied the attention of operators and pathologists since the pioneer days of gastric surgery. Lengemann[1] studied the regional lymphatic glands* which were removed with specimens of carcinoma of the stomach in the clinic of Mikulicz. Renner,[2] in the same clinic, studied the lymphatic involvement in gastric carcinoma in 15 cases which came to autopsy. Cuneo[3] studied carcinomatous stomachs from 8 autopsies in cases which had not been operated on, 1 case at autopsy in which a gastro-enterostomy had been done, and 13 cases in which gastrectomy had been performed. The last observer paid special attention to the lymphatic system of the wall of the stomach and the lymphatic glands, which he studied by means of a modification of Gerota's[4] method of injecting the lymph-spaces and vessels (Fig. 6).

Lengemann[1] and Renner[2] charted the involved glands in a manner somewhat similar to that adopted for this series.

The material for this investigation, which is a continuation of a study made on gastric ulcer by the writer,[5] consists of 200 specimens which had been resected or excised from the carcinomatous stomach. Each specimen was examined immediately after its removal and again in a fixed condition. The location and size of the primary lesion and the location and the relative size of the lymphatic glands of the lesser and greater curvatures were noted and recorded upon diagrams (see charts). One half of each gland was numbered and fixed in 4 per cent. formaldehyd solution (10 per cent. formalin), frozen, cut, and stained with hematoxylin and eosin. All lymphatic glands were examined microscopically and the diagnosis recorded on its respective diagram (see charts). Lymphatic glands which were found to be inflammatory without carcinomatous involvement were examined several times in order to rule out the possibility of involvement in some other portion of the block than the one examined. Absolute accuracy would depend, however, upon serial section of each gland. This is not feasible in a large series of specimens. One thousand four hundred and four lymphatic glands were examined. During the microscopic investigation photographic records were made.

---

* The term "lymphatic glands (lymphoglandulæ)" has been adopted by the writer according to the nomenclature recommended by the "Anatomische Gesellschaft" at the ninth meeting in Basel, and published under the title, "Die anatomische Nomenclatur (Nomina Anatomica)," by Wilhelm His,[15] Leipzig, Verlag von Veit and Comp, 1895.

A clearer conception of the material of this paper may be obtained by first reviewing the results of a previous study by the writer[5] of the same material to determine the character of the process of ulceration in the wall of the stomach. Two hundred and sixteen resected or excised specimens of the stomach were examined. These consisted of simple ulcers, ulcers associated with carcinoma, and carcinoma so advanced that its development upon ulcer could not be determined. In a study of this material it was seen that an initial erosion or partial destruction of the gastric mucosa occurred as the apparent forerunner of extensive ulceration. Why and how the initial disturbance occurred was undetermined. The process of destruction after the initial lesion had occurred was, however, apparent in many of its phases.

It has been shown that gastric ulcers sometimes become healed—scars of old ulcerations having frequently been found at autopsies in general hospitals. Why all gastric ulcers do not heal spontaneously remains an unanswered question. In the previous investigation it was noted that lesions apparently continued with gradual deepening of the ulcer. In many cases this seemed to occur very slowly or periodically. The chronicity of these lesions was shown from the fact that changes, such as the presence of dense scar tissue, lymphocytic infiltration, epithelial hyperplasia, and glandular distortion occurred in practically all ulcers seen in the series. The clinical course of all cases which were studied also bore out their chronic character. It was also found that the base of a gastric ulcer might consist of any of the coats of the stomach (mucosa, muscularis mucosæ, submucosa, muscularis subserosa, or peritoneum). These were often greatly distorted by marked inflammatory reactions. Various stages of extension of gastric ulceration through the wall may be seen in Figs. 1 and 2 (*a*, *b*, and *c*).

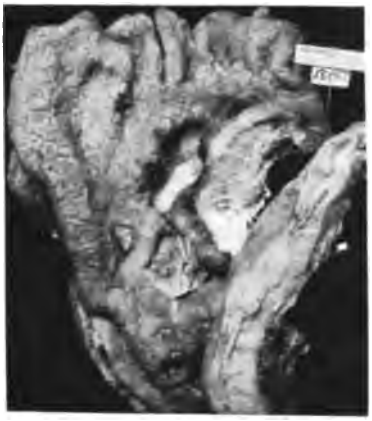


Fig. 1.—Case 18088, Group III. Multiple gastric ulcers, showing them in various stages.

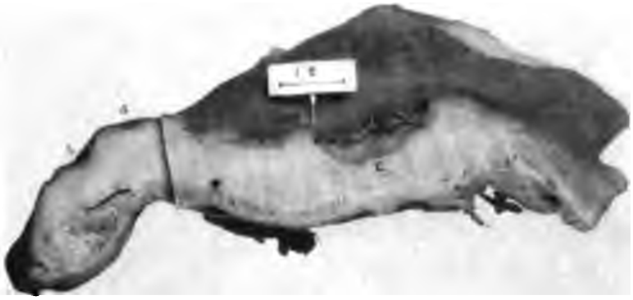


Fig. 2.—Case 18088, Group III. Gross section through the ulcers in Fig. 1: *a*, Small ulcer of the mucosa; *b*, ulcer invading the submucosa; *c*, largest ulcer, showing the dense scar tissue in the muscular wall and extending to the serosa.

The border of the mucosa in such specimens was almost invariably hypertrophic; the gastric glands were distorted and often cystic or dilated (Figs. 3 and 4). The epithelial cells were in a condition of hyperplasia; in simple ulcers these cells had attained morphologic development and perhaps their physiologic differentiation. The last two features serve well as an aid in the differentiation between inflammatory or simple irritative epithelial hyperplasia, and the apparently morphologically and physiologically undifferentiated epithelial hyperplasia of carcinoma. In the latter condition the cells were found to be passing through stages similar to those described in carcinoma of the breast.[6] They invaded surrounding tissues only when they were morphologically undifferentiated.

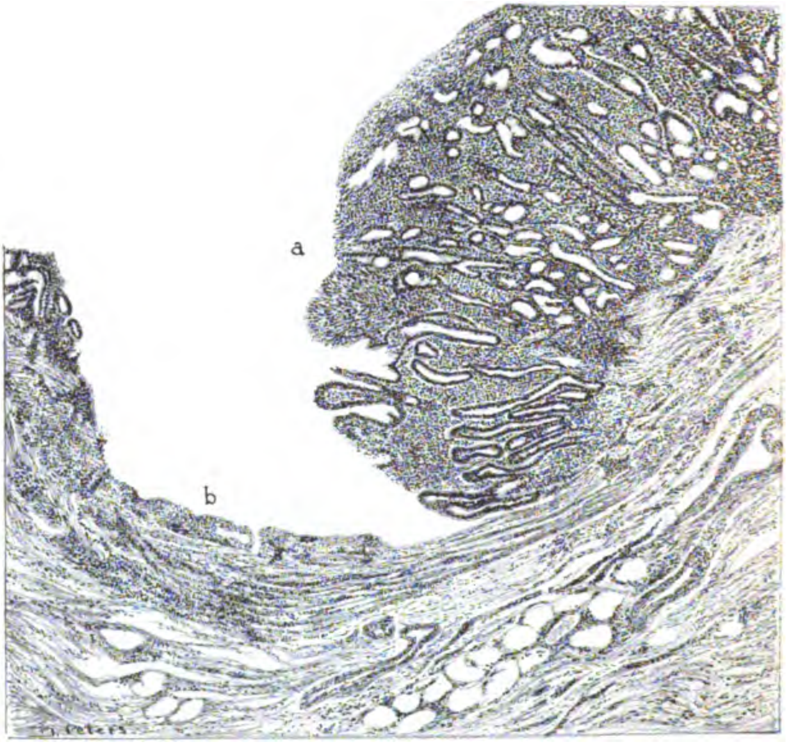


Fig. 3.—Case 25692. Microscopic section through the border of a simple gastric ulcer with a characteristic border and base: *a*, Hypertrophic mucosa; *b*, dense scar tissue base.

The underlying coats of the stomach and the base of the ulcer apparently became secondarily involved from some point in the mucosa. Epithelial cells apparently entered the lymphatic spaces of the mucosa and followed the channels described by Cunéo,[3] Sappey,[7] and Most.

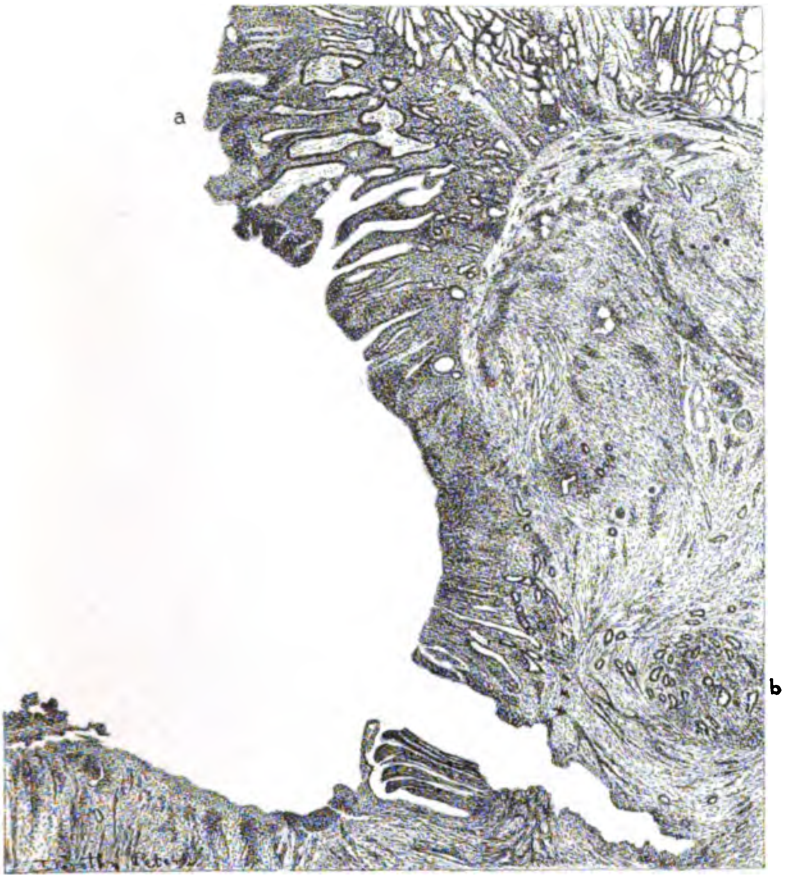


Fig. 4.—Case 21555. Microscopic section through the carcinomatous border of a gastric ulcer: *a*, Hypertrophic mucosa, cystic and hypertrophic glands; *b*, invading glandular elements in the submucosa.

According to Cunéo,[3] the lymphatic spaces between the gastric glands (Fig. 6) are intercommunicating, form large spaces in the submucosa, pass through the musculature, collect in the subserosa, and enter lymphatic channels just under the peritoneum. This gastric intramural lymphatic system empties its contents into the extramural or regional lymphatic glands. The glands of the specimens in this series are divided, according to Cunéo's classification, into the lesser curvature, subpyloric, retropyloric, and greater curvature groups (Fig. 5).

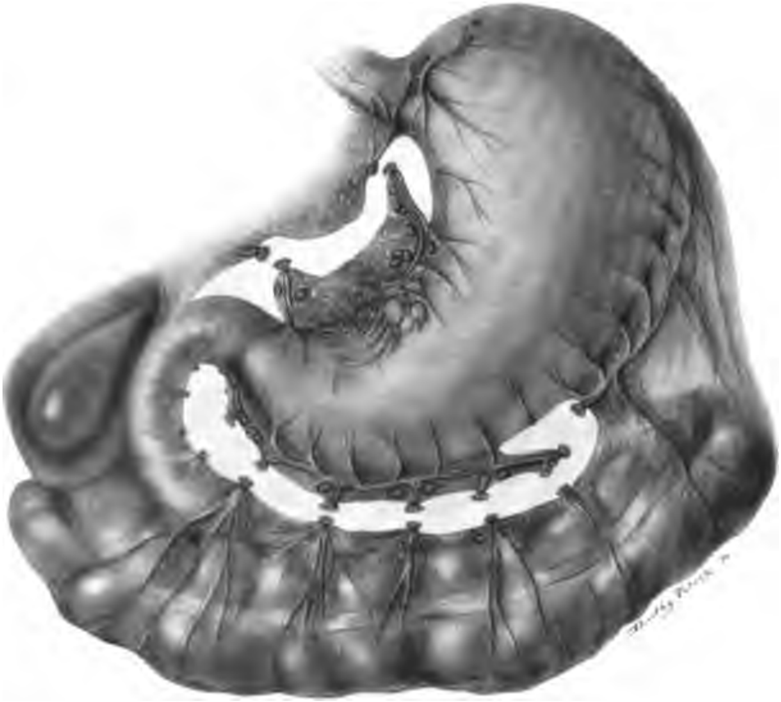


Fig. 5.—Portion of the stomach usually resected, showing the location of the glands investigated in this study (Mayo).

The relation of the primary lesion—carcinoma—to the amount of lymphatic involvement and the relation of these to the clinical histories were the objects of this investigation, which is a part of a general investigation of gastric ulcer and gastric carcinoma by the writer.

Primary lesions varied from 1 cm. to 14 cm. in diameter and from 1 cm. to 5 cm. in depth. Such a series of specimens, showing carcinoma in many stages, allows one to consider the accompanying degrees of lymphatic reaction. After the condition of the glands was charted the specimens and charts divided themselves into three groups: Group I contained specimens in which no carcinomatous lymphatic glandular involvement was found; in Group II there was some glandular involvement, and in Group III all the specimens showed carcinomatous glandular involvement.

Lesions which were 9 cm. in diameter and 3 cm. in depth occurred in Group I, a fact which demonstrates that carcinomatous cells in the stomach do not always enter the lymphatic glands with the same rapidity nor at any apparent definite stage in their development.

Small ulcerations—2 cm. in diameter and 2 cm. in depth—with carcinomatous borders occasionally showed complete glandular involvement. From these figures alone it may be seen that one should not judge the condition of the lymphatics by the size of the primary lesion. There is apparently no direct relation between the size of the primary lesion and the glandular involvement. Large tumors exist without carcinomatous glandular involvement, and small tumors exist with extensive carcinomatous glandular involvement. The surgeon should, therefore, be guided by the microscopic examination of regional glands. Macroscopic diagnosis, as pointed out by Lengemann,[1] Renner,[2] Cunéo,[3] and others, has little value, because glands which are grossly inflammatory often contain microscopic carcinomatous involvement.

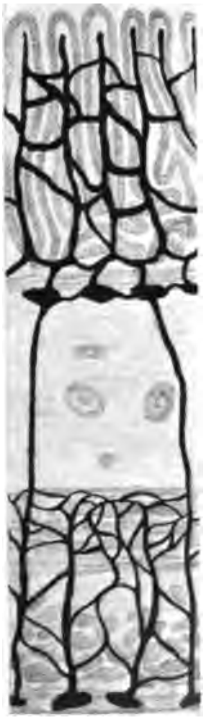


Fig. 6.—Diagram of wall of human stomach, showing injected lymphatic channels (from Cunéo).

Resected gastric specimens contained from 1 to 15 lymphatic glands* in the lesser curvature and from 1 to 13 in the greater curvature. The average in the lesser curvature was 2.9 and the greater curvature 5.1. They varied in size from 2 mm. to 2 cm. in their long diameters, and from 2 mm. to 1.5 cm. in their short diameters. Their size had no apparent relation to the size of the lesion, duration of dyspepsia, duration of acute symptoms, age, nor sex.

The 200 specimens examined contained 1404 lymphatic glands. Fifty-two per cent. of these were carcinomatous. This figure agrees almost exactly with the percentage reported by Lengemann,[1] who found 42 per cent. of 302 lymphatic glands involved, and by Renner,[2] who reports 50 per cent. of 78 lymphatic glands of the subpyloric group carcinomatous.

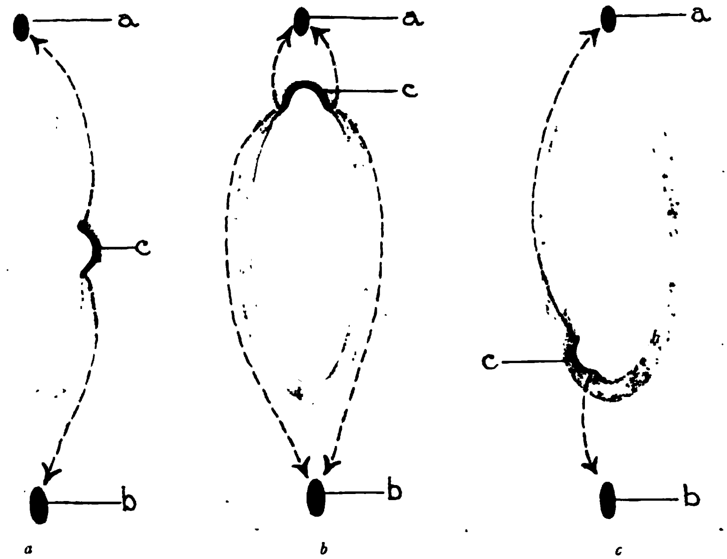


Fig. 7.—Diagrams of transverse sections of the wall of the stomach, showing hypothetic carcinomatous ulcers (*c*) and the directions of the resultant carcinomatous invasion of the lymphatic glands (*a*, *b*).

---

* Specimens which were removed several years ago when no attempt was made to remove all the lymphatic glands in cases which were resected palliatively show usually a small number of glands. These cases reduce the general average in this paper.

Large lymphatic glands may be inflammatory, and small glands may be carcinomatous (see charts). The color, shape, size, and consistence of a lymphatic gland are not varied by the presence of one or two groups of carcinomatous cells in a sinus. Gross diagnoses are of value only in extensive involvement.

Inflammatory lymphatic hyperplasia (Figs. 8 and 9), which was found in many stages of its development in non-carcinomatous (Fig. 8) and carcinomatous (Fig. 9) glands, is most important to the surgical pathologist, whose duty it is to differentiate lymphocytoblastic cells, endothelial cells, and large mononuclear lymphocytes in a hyperplastic lymphatic gland from isolated epithelial cells in the lymphatic sinuses. Differentiation for operative purposes should not be attempted by a pathologist of meager experience. Groups of epithelial cells (Fig. 9) in the lymphatic glands should be the criterion of carcinomatous involvement. Large cells are often seen in the sinuses (Fig. 8, *d* and *f*, and Fig. 9, *a* and *b*); some are exfoliated endothelial cells; others are doubtless macrocytes. One cannot always say that they are not epithelial cells (Fig. 9, *c*, *d*, *e*, and *f*). In a lymphatic gland which is extremely hyperplastic the germinal centers present cells (lymphocytoblastic) which are variable in size and shape; these are so irregular that it is practically impossible to distinguish them from the irregular epithelial cells of carcinoma.

The cells of carcinoma are found in the peripheral or subcapsular sinues early in lymphatic involvement, as has been previously noted by Billroth,[9] Bozzolo,[10] Rindfleisch,[11] Orth,[12] Zender,[13] Petrick,[14] and Cuneo.[3] They may be single or in groups (Fig. 9). They may invade the tissues surrounding the sinuses. The gland may become filled with dense connective tissue which may also become invaded. The cells occasionally penetrate the glandular capsule and invade the surrounding fat.

A detailed history of each of 200 cases would occupy more space than was intended for this paper. It must, therefore, be sufficient to state briefly their positive and negative relation to glandular involvement.

The average ages in Groups I, II, and III are respectively 50.8

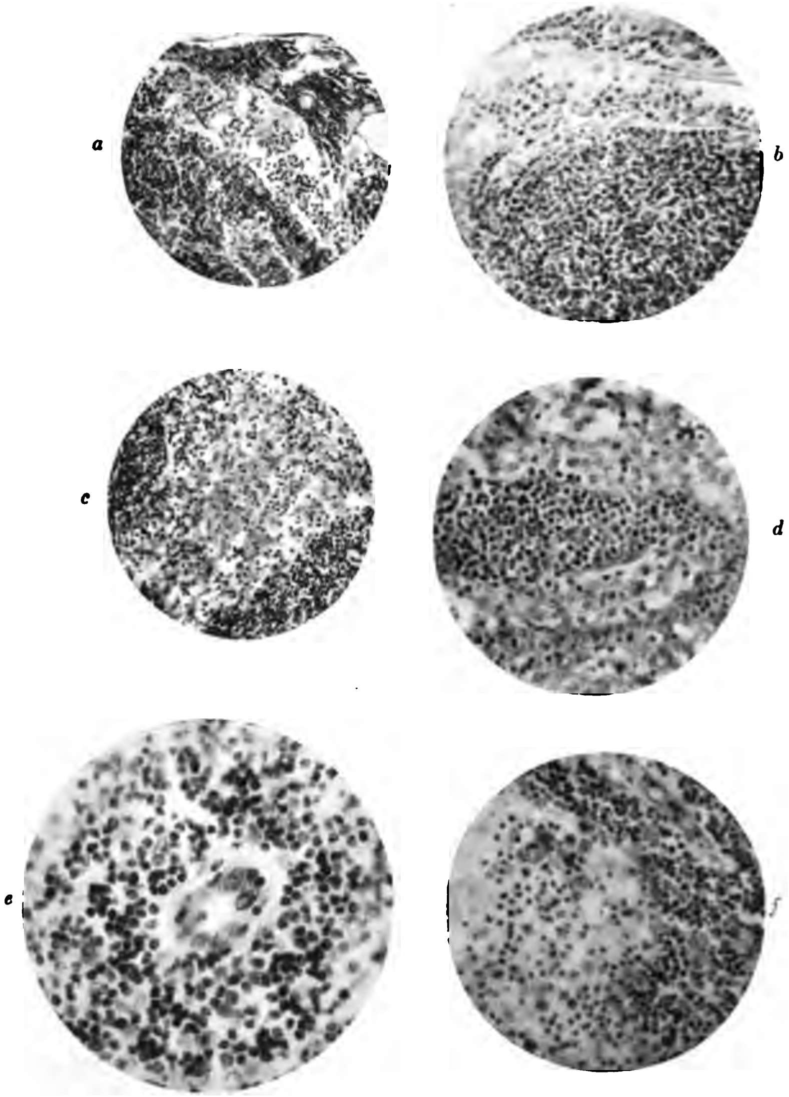


Fig. 8.—*a*, Section showing a sinus of a lymphatic gland filled with lymphocytes and coagulated lymph; *b*, sinus in the deeper structure of a lymphatic gland; *c*, sinus filled with lymphocytes and exfoliated endothelial cells; *d*, sinuses containing coagulated lymph, lymphocytes (darkly stained), and endothelial cells (faintly stained); *e*, large endothelial cells lining a vessel which may be confused with groups of epithelial cells in carcinomatous invasion; *f*, sinus filled with lymphocytes, coagulated lymph, and large cells. The largest cell in the field is probably an epithelial cell.

UNIV. OF CALIFORNIA

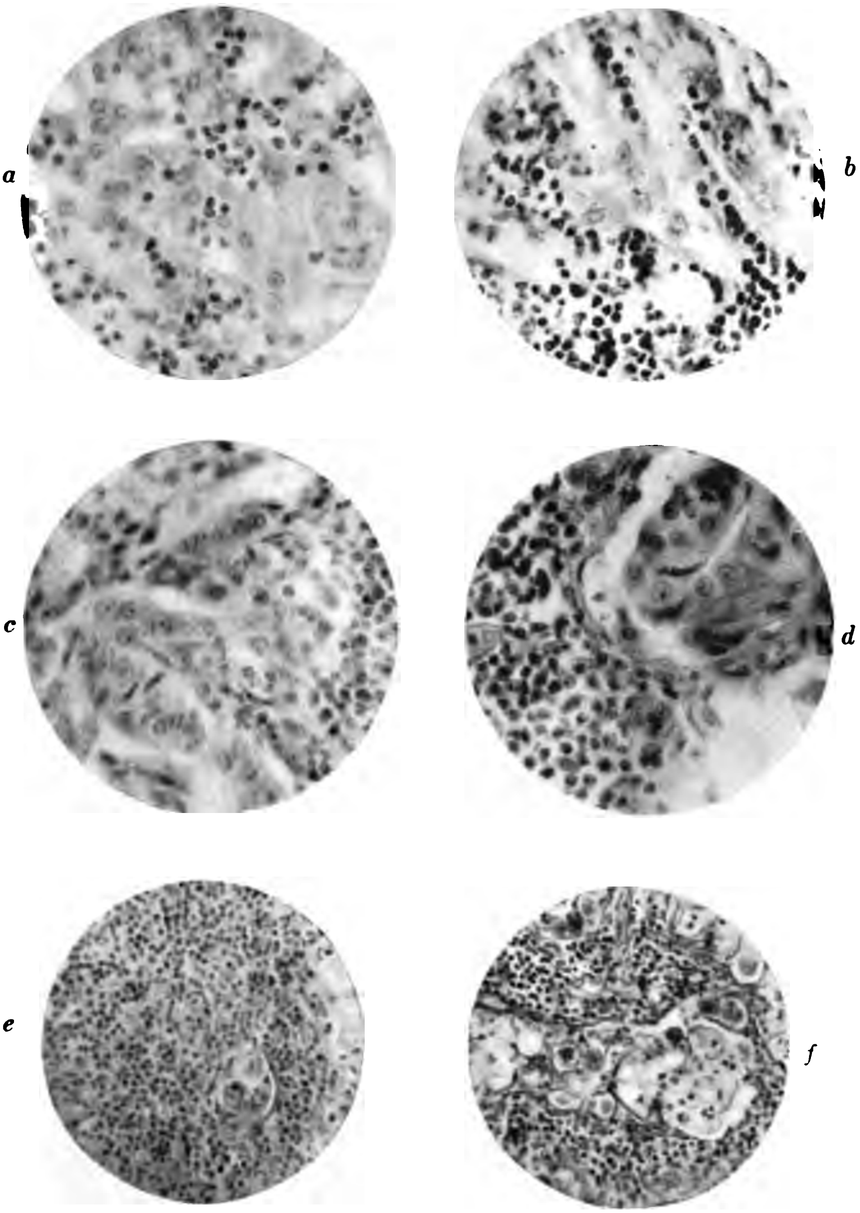


Fig. 9.—*a*, Lymph sinus containing large cells with clear pale nuclei. The lymphocytes are much darker. The exact denomination of these cells is extremely difficult. They are probably carcinoma cells in this case, although it is impossible to be absolutely certain. *b*, Lymph sinus containing large pale cells, the diagnosis of which is uncertain (the nuclei, when compared to those in Fig. 9, *c*, show marked similarity); *c*, carcinoma in lymph sinus (this picture should be compared to Fig. 9, *b*); *d*, carcinoma in lymph sinus; *e*, Degenerating epithelial cells surrounded by lymphocytes; *f*, carcinoma. The epithelial cells are large, apparently degenerating, and contain leukocytes.

UNIV. OF CALIFORNIA

years, 51.7 years, and forty-six years, which show no apparent relation between the amount of lymphatic involvement and the age of the patient when seen at operation. In the third group (extensive involvement) the average age is five years younger than the second group (partial involvement), which suggests a more rapid progress in younger individuals. The difference, however, is not sufficiently great to allow such conclusions. The extreme ages at which carcinoma of the stomach was found in this series are thirty and eighty-three years, a fact which adds another point to free our minds of the old clinical adage that carcinoma is a disease of middle life.

The history of gastric disturbances of a mild or intermittent nature, which have extended over a long period, may have some etiologic relation to ulceration of the gastric mucosa. This feature was studied in the three groups without finding results of positive value. The duration of dyspepsia extended over average periods of 8.5 years, 8+ years, and 8+ years in the three groups.

Seventy-three per cent. of all cases were in males and 27 per cent. in females, a ratio which remains practically the same in the three groups—a fact which demonstrates that sex plays no apparent rôle in influencing the amount of involvement.

Acute gastric disturbances existed in Groups I, II, and III, respectively 17.2 months, 12.5 months, and 17.4 months.

A consideration of clinical facts carries with it many difficulties. Loss of weight, for example, may be due to dietary starvation, gastric secretory inactivity, gastric motor insufficiency, pyloric obstruction, or toxemia. Whether or not one or more of these is the cause of the loss of weight in these cases, the fact remains that in Group I the average loss of weight was 25 pounds; Group II, 28.4 pounds; Group III, 42.5 pounds. In the absence of pyloric obstruction the amount of reduction in weight may be an approximate clinical index of glandular involvement.

Another point of interest to the clinician and surgeon from a prognostic standpoint is the immediate post-operative hospital mortality in reference to the amount of glandular involvement at operation. The groups presented the following figures: Group I, 7.6 per cent.; Group II, 11.6 per cent.; Group III, 18.7 per cent. The parallel increase between the amount of glandular involvement and the hospital mortality may be indicative only of reduction of general resistance or local tissue reparative reduction in extensive carcinoma.

The subsequent mortality also varied in the different groups. The percentage of the cases which were alive one, two, and three years after resection was higher in the cases without glandular involvement. Thirty-eight and four-tenths per cent. of all the patients of which some knowledge was obtained were dead.

The findings of this investigation have positive and negative value. They are, however, of greatest value in supplying the macroscopic and gross microscopic findings in a large series of specimens examined under fresh conditions at operation and confirmed by fixed tissue.

The negative conclusions may be summarized as follows:

1. The size of regional lymphatic glands bears no apparent relation to the size of the primary lesion in the stomach.

2. The size of a lymphatic gland is no criterion of the presence or absence of carcinoma.

3. Gross diagnoses of lymphatic glands are of no value except in advanced carcinoma of the glands.

4. The duration of symptoms bears no apparent relation to the size and extent of involvement in the lymphatic glands.

5. The average age at operation and sex bear no direct relation to the glandular involvement.

The positive conclusions may be summarized as follows:

1. The average loss of weight increases with the increase in extent of glandular involvement.

2. The immediate hospital post-operative mortality is in direct proportion to the amount of glandular involvement.

3. The subsequent mortality is in direct proportion to the amount of glandular involvement.

4. Carcinomatous glandular involvement is very often microscopic.

5. The surgeon who desires to treat early carcinoma must

depend upon the microscope in the hands of an experienced pathologist for early carcinomatous lymphatic involvement.

6. The diagnosis of early carcinomatous involvement requires extensive experience in the study of the so-called precarcinomatous reaction of lymphatic glands.

LITERATURE

1. Lengemann: "Die Erkrankungen der regionären Lymphdrüsen beim Krebs der Pars pylorica der Magens," "Arch. f. klin. Chir.," vol. lxviii.
2. Renner: "Die Lymphdrüsen-Metastasen beim Magen-Krebs," "Mitteil. a. d. Grenzgebieten d. Medizin u. Chir.," vol. xiii.
3. Cunéo: "De l'envahissement du système lymphatique dans le cancer de l'estomac," "Thèse de Paris," 1900.
4. Gerota: "Zur Technik der Lymphgefäss-Injection; eine neue Injectionsmasse für Lymphgefässe; Polychrome Injection," "Anatomische Anzeiger," 1896, vol. xii.
5. MacCarty: "Pathology and Clinical Significance of Gastric Ulcer," "Surgery, Gynecology and Obstetrics," May, 1910, vol. x.
6. MacCarty: "Carcinoma of Breast," "Old Dom. Med. Jour.," 1910, vol. xii, "Trans. of Southern Surgical and Gynæcological Assoc.," 1910, vol. xxiii, and monograph in the process of preparation.
7. Sappey: "Anatomie, Physiologie, Pathologie des vaisseaux lymphatiques, considérés chez l'homme et les vertébrés," Paris, 1874.
8. Most: "Über die Lymphgefässe und die regionären Lymphdrüsen des Magens in Rücksicht auf die Verbreitung der Magencarcinome," "Verhandlung d. deutsch. Gesellsch. f. Chir.," 28. Kong., 1899, vol. ii.
9. Billroth: "Neue Beobachtungen über die feinere Struktur pathologisch-veränderter Lymphdrüsen," "Virchow's Archiv," 1861, vol. xxi, p. 423.
10. Bozzolo: Über die Verbreitung der Krebsneubildungen in den Lymphdrüsen," "Centralbl. f. d med. Wiss.," 1876, vol. xiv, p. 341.
11. Rindfleisch: "Trait. d'hist. Path. Trad. franc," 1888.
12. Orth: "Lehrbuch der spez. path. Anat.," 1887.
13. Zender: "Über Krebsentwicklung in Lymphdrüsen," Virchow's Archiv," 1890, vol. cxix, p. 261.
14. Petrick: "Über die Verbreitung des Carcinoms den Lymphdrüsen," "Deut. Zeitschr. f. Chir.," 1891, vol. xxxii, p. 530.
15. His: "Die anatomische Nomenclatur (Nomina Anatomica)," Verlag v. Veit u. Comp., 1895.

GROUP I

Case No.	Total No. Glands	Total No. Glands Lesser Curvature	Total No. Glands Greater Curvature	Total No. Glands Lesser Curvature Involved	Total No. Glands Greater Curvature Involved	Case No.	Total No. Glands	Total No. Glands Lesser Curvature	Total No. Glands Greater Curvature	Total No. Glands Lesser Curvature Involved	Total No. Glands Greater Curvature Involved
16806	5	4	1	0	0	31739	3	0	3	0	0
16884	3	2	1	0	0	32018	6	0	6	0	0
17139	1	1	0	0	0	32273	10	1	9	0	0
17424	1	1	0	0	0	33109	4	0	4	0	0
17586	2	0	2	0	0	33226	10	4	6	0	0
17835	3	0	3	0	0	33255	7	1	6	0	0
18271	1	0	1	0	0	33363	11	2	9	0	0
20367	5	0	5	0	0	33621	9	2	7	0	0
20468	5	2	3	0	0	35572	3	3	0	0	0
20887	4	1	3	0	0	35590	7	2	5	0	0
21965	3	2	1	0	0	35970	3	0	3	0	0
22289	4	2	2	0	0	36489	7	2	5	0	0
22314	5	1	4	0	0	36649	10	2	8	0	0
22925	2	2	0	0	0	37070	3	3	0	0	0
23374	4	4	0	0	0	37080	6	1	5	0	0
23651	11	1	10	0	0	37265	6	2	4	0	0
24277	4	1	3	0	0	37340	8	1	7	0	0
24712	4	0	4	0	0	37392	3	2	1	0	0
24909	14	5	9	0	0	37873	3	2	1	0	0
25449	6	2	4	0	0	40013	9	3	6	0	0
26273	10	4	6	0	0	40930	6	2	4	0	0
27208	6	1	5	0	0	41081	1	0	1	0	0
27365	4	2	2	0	0	41223	7	1	6	0	0
27831	4	0	4	0	0	41511	5	5	0	0	0
28004	1	1	0	0	0	41804	3	0	3	0	0
28105	6	2	4	0	0	41966	6	1	5	0	0
28294	8	0	8	0	0	42143	9	1	8	0	0
28358	13	2	11	0	0	42151	3	2	1	0	0
29322	8	2	6	0	0	43400	7	3	4	0	0
30060	7	3	4	0	0	43698	6	2	4	0	0
30363	9	2	7	0	0	Spec. C.	5	0	5	0	0
30809	6	0	6	0	0	26751	6	4	2	0	0
30824	6	4	2	0	0						

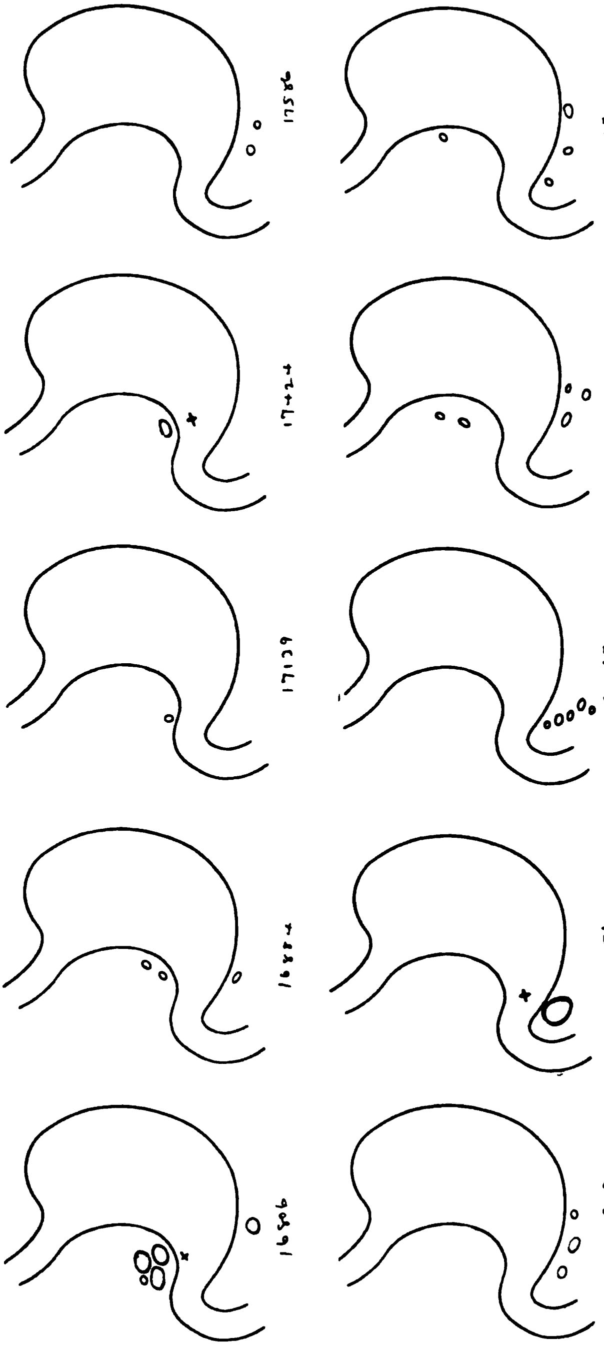


CHART I.—GROUP I: DIAGRAMS OF SPECIMENS WITH NO CARCINOMATOUS GLANDULAR INVOLVEMENT. INFLAMMATORY GLANDS ARE WHITE.

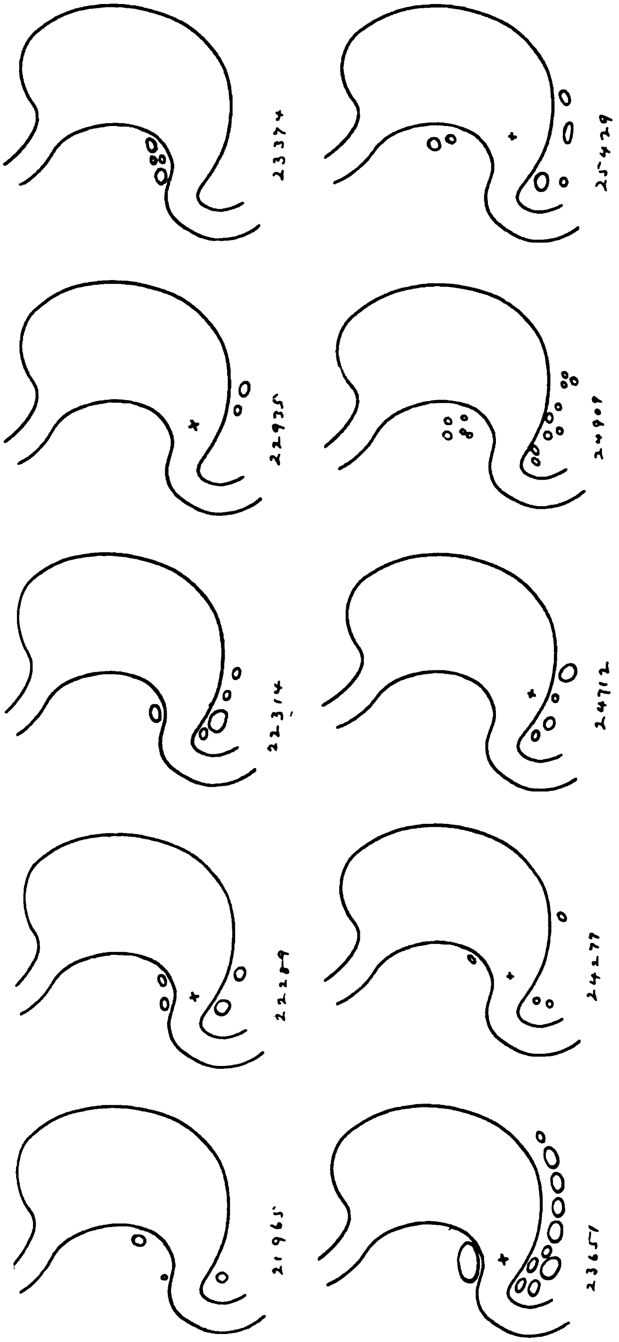


CHART I.—(*Continued.*)

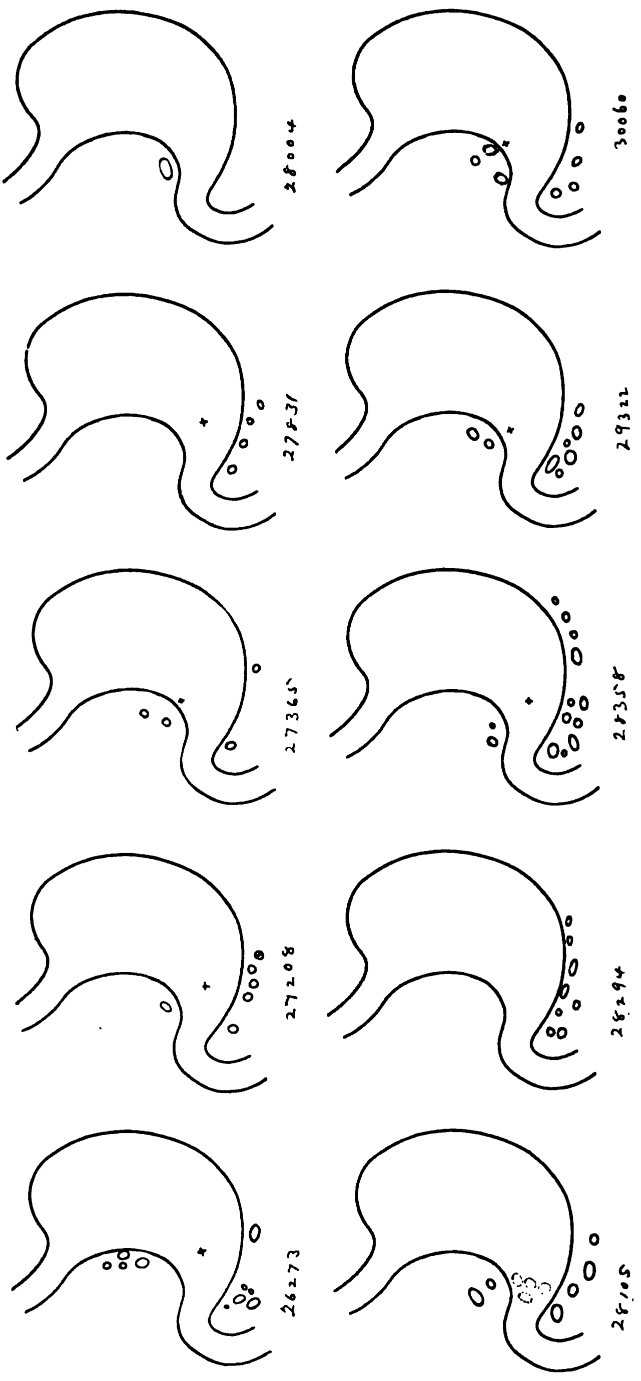


CHART I.- (*Continued.*)

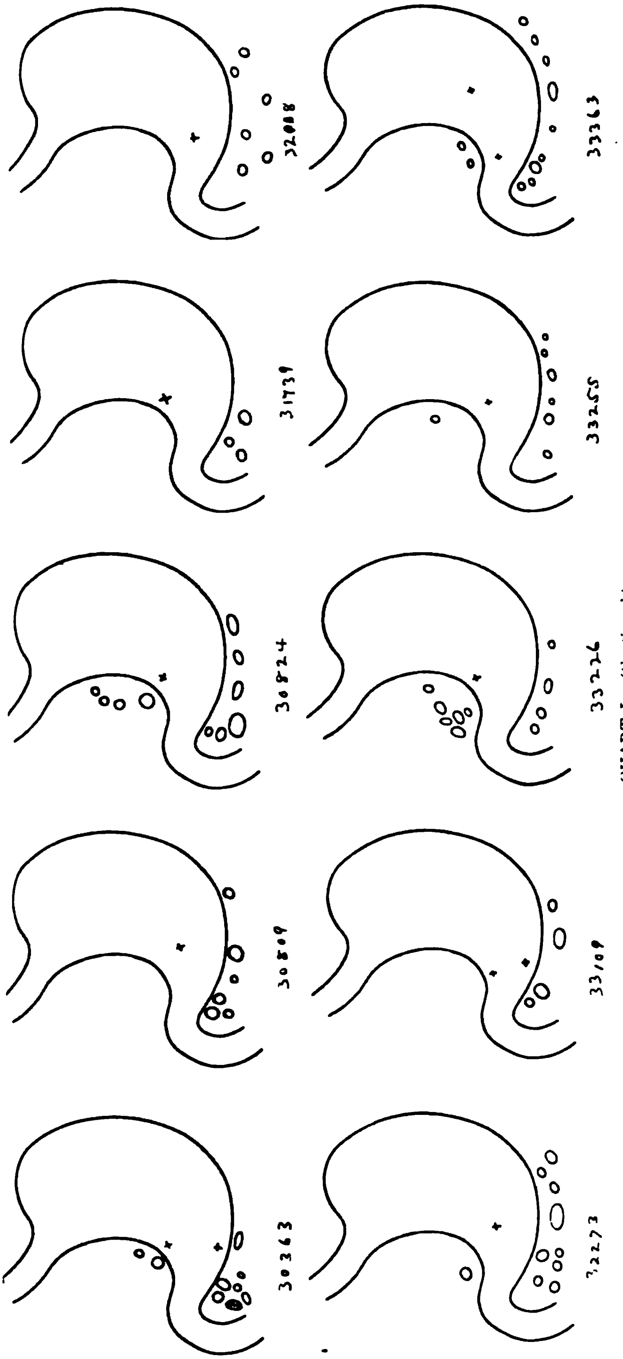


CHART I.—(Continued.)

(Continued)

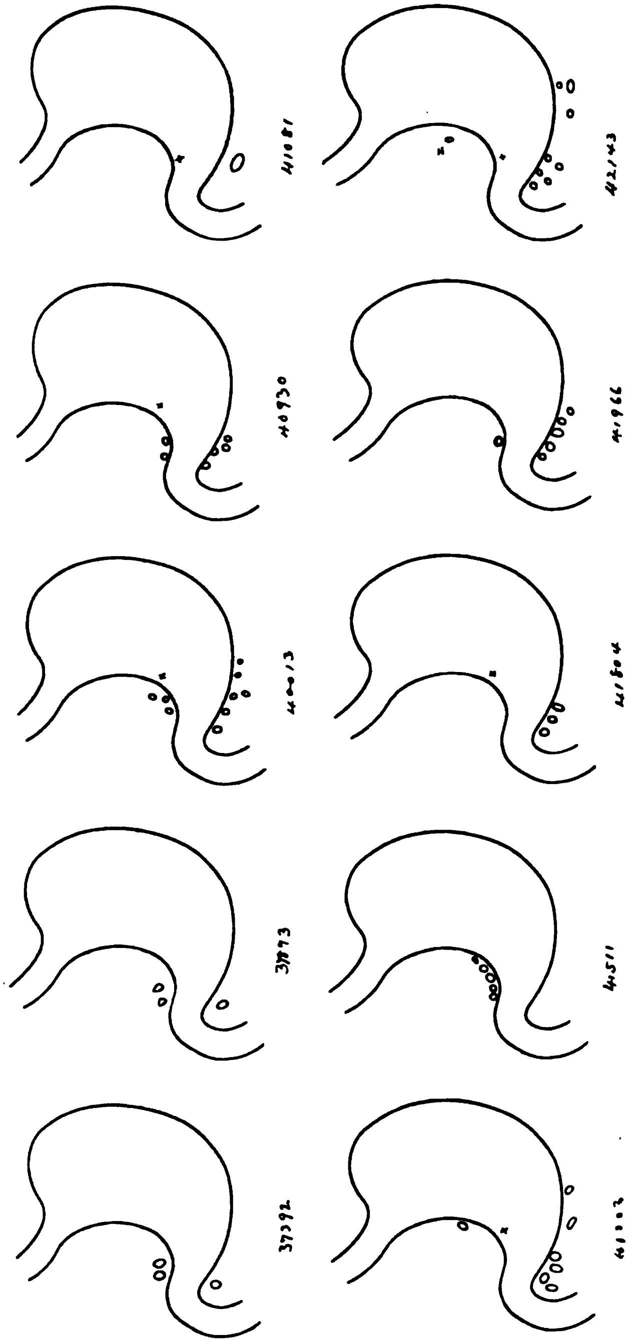


CHART I.—(*Continued.*)

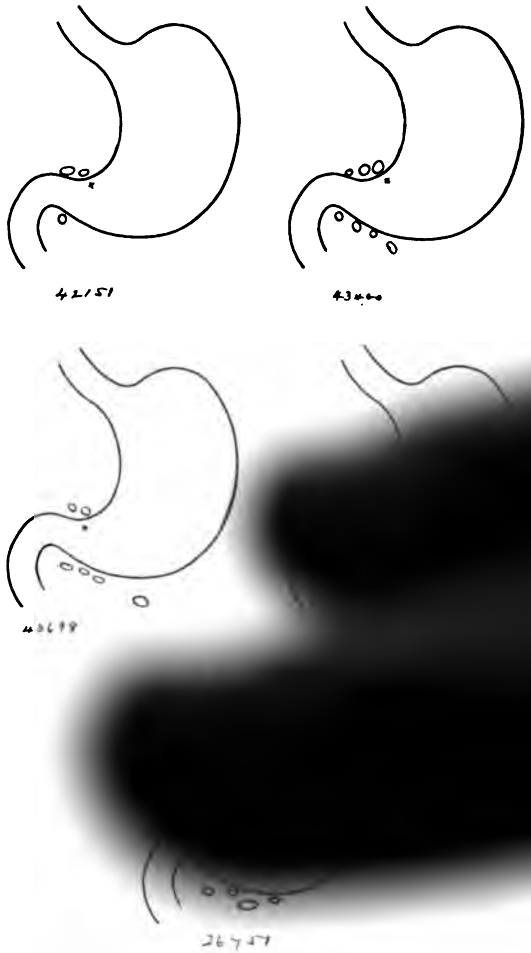


CHART I.—(*Continued.*)

GROUP II

Case No.	Total No. Glands	Total No. Glands Lesser Curvature	Total No. Glands Greater Curvature	Total No. Glands Lesser Curvature Involved	Total No. Glands Greater Curvature Involved	Case No.	Total No. Glands	Total No. Glands Lesser Curvature	Total No. Glands Greater Curvature	Total No. Glands Lesser Curvature Involved	Total No. Glands Greater Curvature Involved
15351	6	4	2	4	1	31325	6	1	5	0	2
15673	8	3	5	0	3	31450	11	3	8	0	2
16553	6	2	4	1	3	31451	10	2	8	1	0
16729	4	0	4	0	2	31746	4	4	0	1	0
16974	7	2	5	1	5	31861	12	4	8	4	4
17319	14	3	11	3	10	31951	8	1	7	0	1
17459	8	4	4	2	2	31969	11	3	8	3	5
17985	6	1	5	0	3	32076	12	2	10	2	2
18597	11	3	8	2	4	32356	18	7	11	6	9
19070	7	2	5	1	2	32359	9	3	6	0	4
19322	8	3	5	1	3	32393	14	1	13	1	6
19376	4	2	2	1	1	32576	13	7	6	2	0
19559	4	1	3	1	2	32367	9	3	6	3	3
19604	14	6	8	2	6	33213	7	1	6	1	3
19832	2	0	2	0	1	33675	11	6	5	0	1
20442	9	4	5	2	4	33956	8	2	6	1	0
20447	9	4	5	2	4	33982	10	3	7	3	3
20623	10	3	7	2	3	33359	10	4	6	4	2
21659	4	1	3	0	1	34431	5	5	0	3	0
21803	13	4	9	3	8	34511	6	4	2	1	1
22001	6	3	3	1	0	35211	11	6	5	0	5
22047	8	1	7	1	5	35389	5	5	0	1	0
22309	10	1	9	0	6	35856	2	1	1	0	1
22973	8	1	7	0	2	36484	11	4	7	3	1
23406	8	4	4	0	1	37193	10	5	5	4	2
23612	6	0	6	0	1	37237	16	6	10	2	7
24382	8	0	8	0	3	37674	8	3	5	1	0
24527	16	3	13	0	4	37876	3	0	3	0	2
24555	9	3	6	1	0	38073	10	2	8	1	2
25550	5	2	3	2	1	38150	11	0	11	0	7
25563	13	2	11	0	8	38368	4	0	4	0	1
26043	9	3	6	2	4	38550	6	0	6	0	1
26541	5	1	4	1	3	39944	13	4	9	2	5
26743	8	3	5	3	4	40742	5	0	5	0	1
26965	8	5	3	4	2	40840	3	0	3	0	2
27209	6	3	3	3	2	41251	7	0	7	0	1
27370	5	0	5	0	2	41342	16	4	12	0	3
27559	6	2	4	1	2	42325	5	2	3	1	3
27734	5	2	3	2	0	42532	3	1	2	1	0
27898	7	3	4	3	3	42990	4	1	3	1	1
28363	9	4	5	2	0	43068	8	8	0	3	0
28189	11	3	8	1	4	43086	5	2	3	2	1
28579	10	5	5	4	4	43180	4	0	4	0	2
28880	13	5	8	5	6	43542	10	1	9	1	8
28936	13	3	10	1	7	43758	10	5	5	5	3
29239	11	5	6	5	2	43894	8	2	6	1	0
29799	8	1	7	0	4	44070	12	2	10	2	5
29904	8	1	7	0	2	44064	5	1	4	0	1
30316	11	1	10	1	4	Spec. A.	13	6	7	2	7
30464	6	1	5	0	1	Spec. D.	9	0	9	0	1
31140	19	5	14	1	2	42585	4 and mass	mass	4	mass ca.	2
31297	11	3	8	0	3						

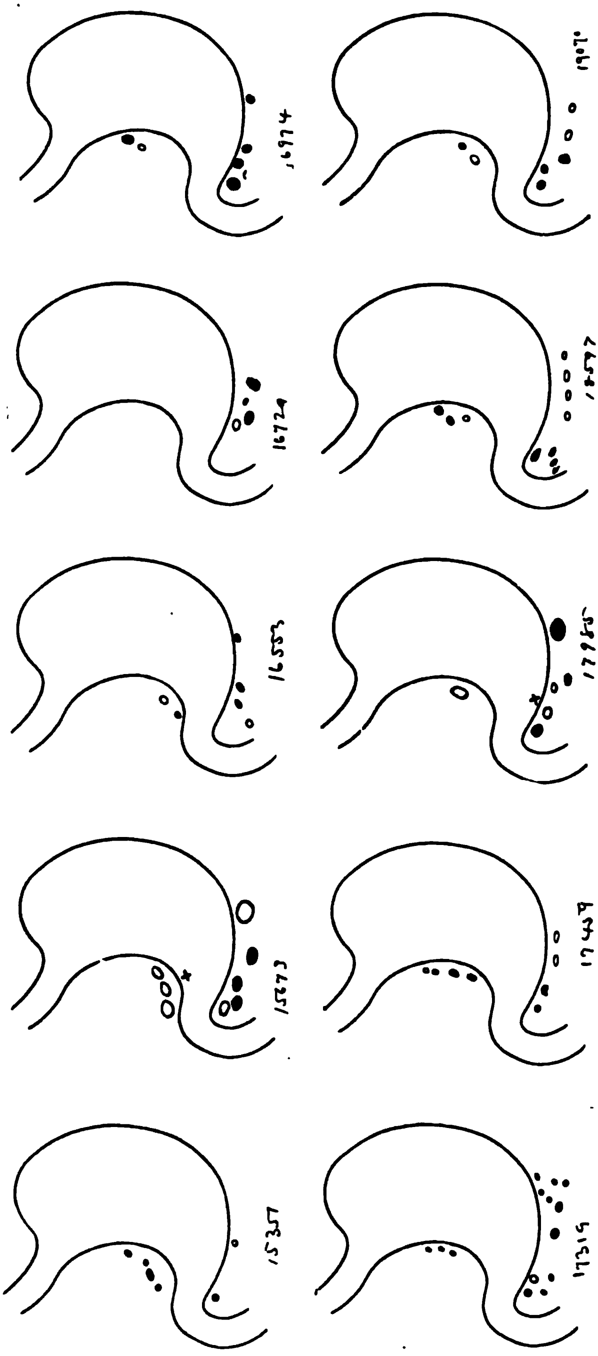


CHART II.—GROUP II: DIAGRAMS OF SPECIMENS WITH SOME CARCINOMATOUS GLANDULAR INVOLVEMENT. CARCINOMATOUS GLANDS ARE SOLID BLACK.

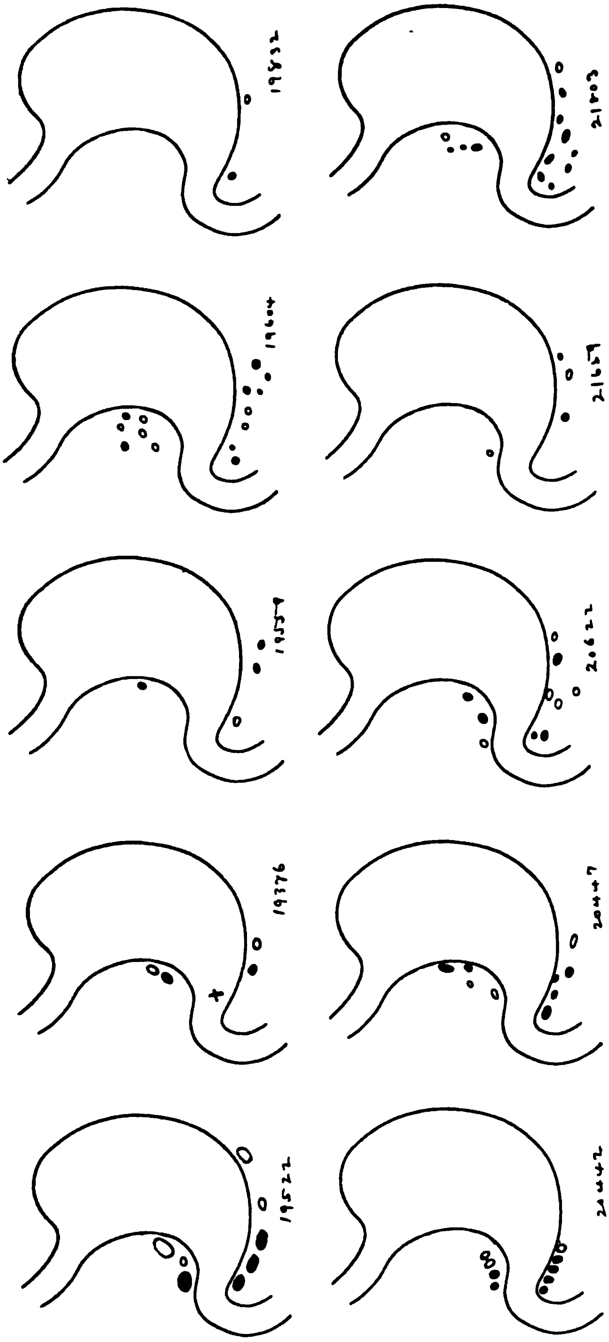


CHART II.—(*Continued.*)

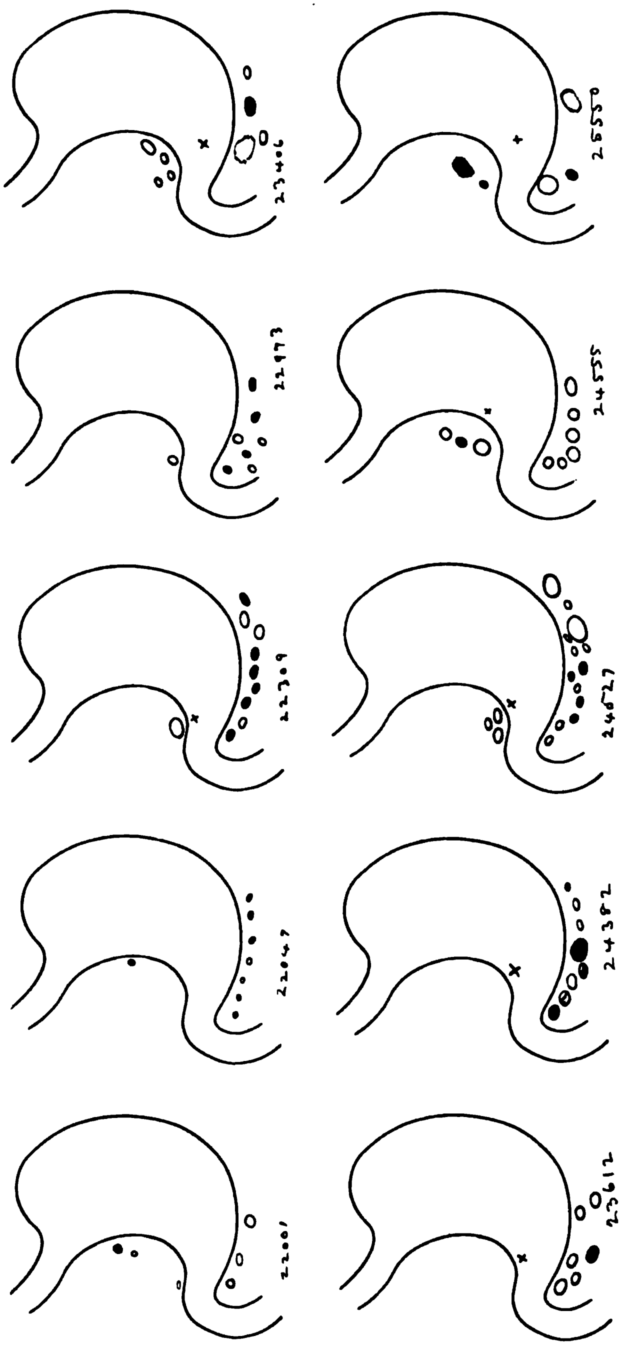


CHART II.—(*Continued.*)

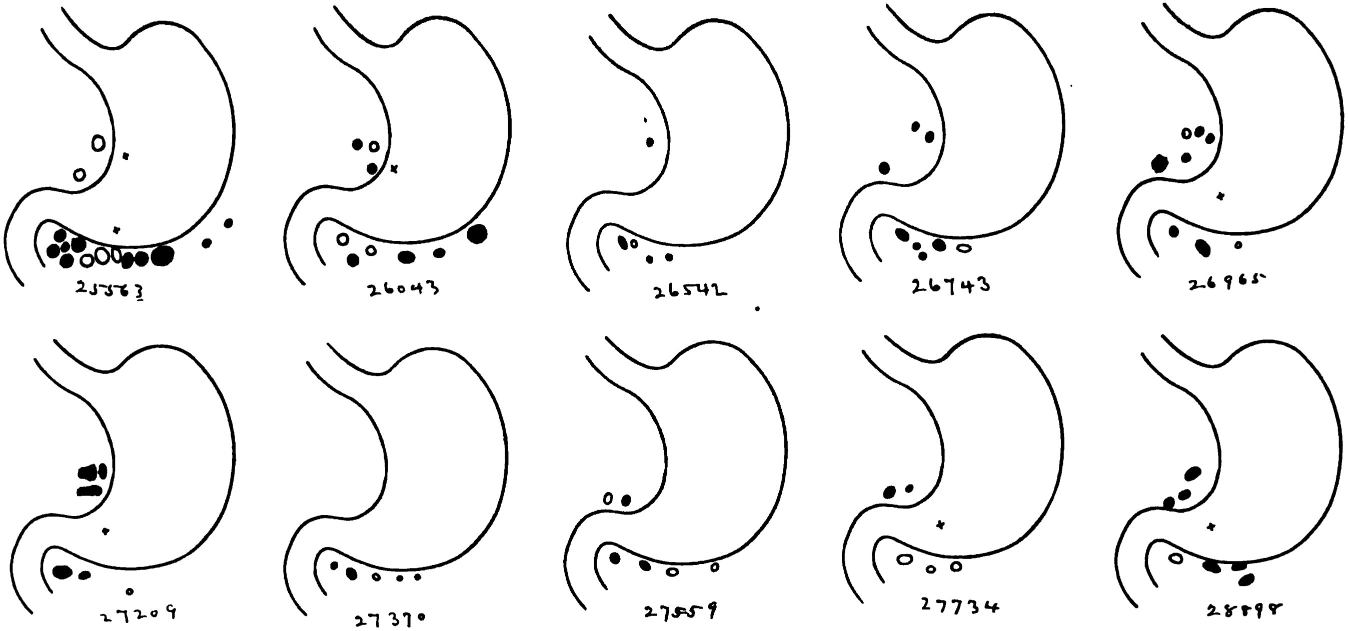


CHART II.—(*Continued.*)

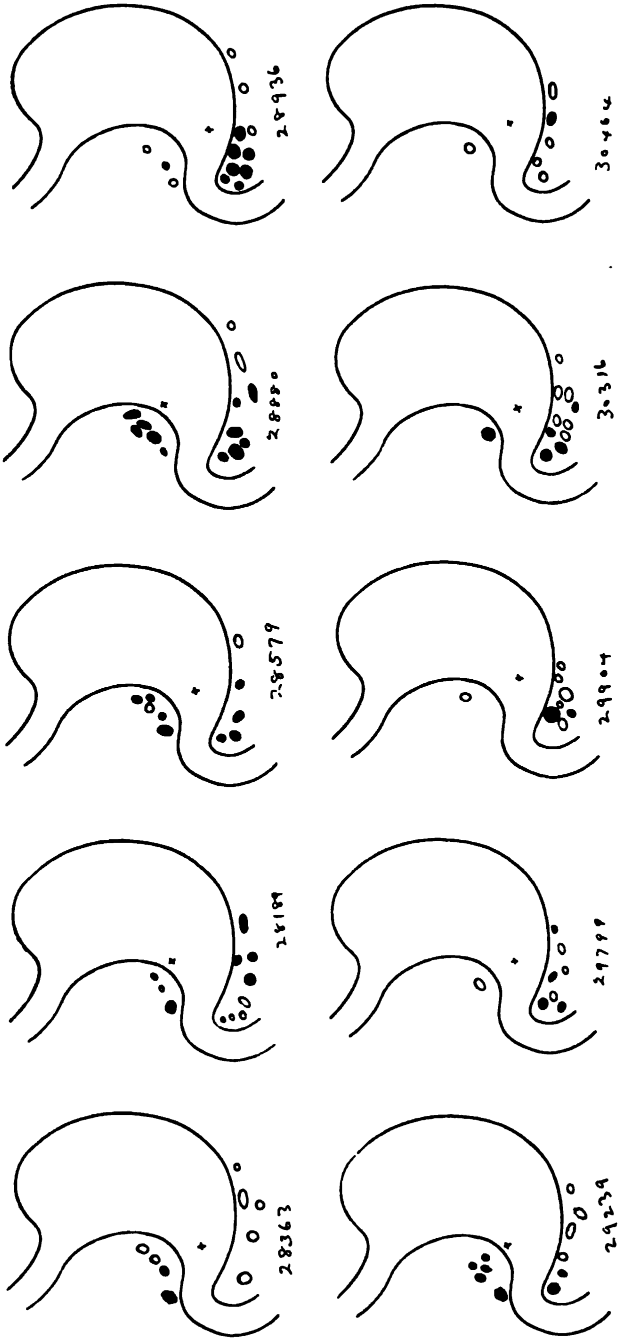


CHART II.—(Continued.)

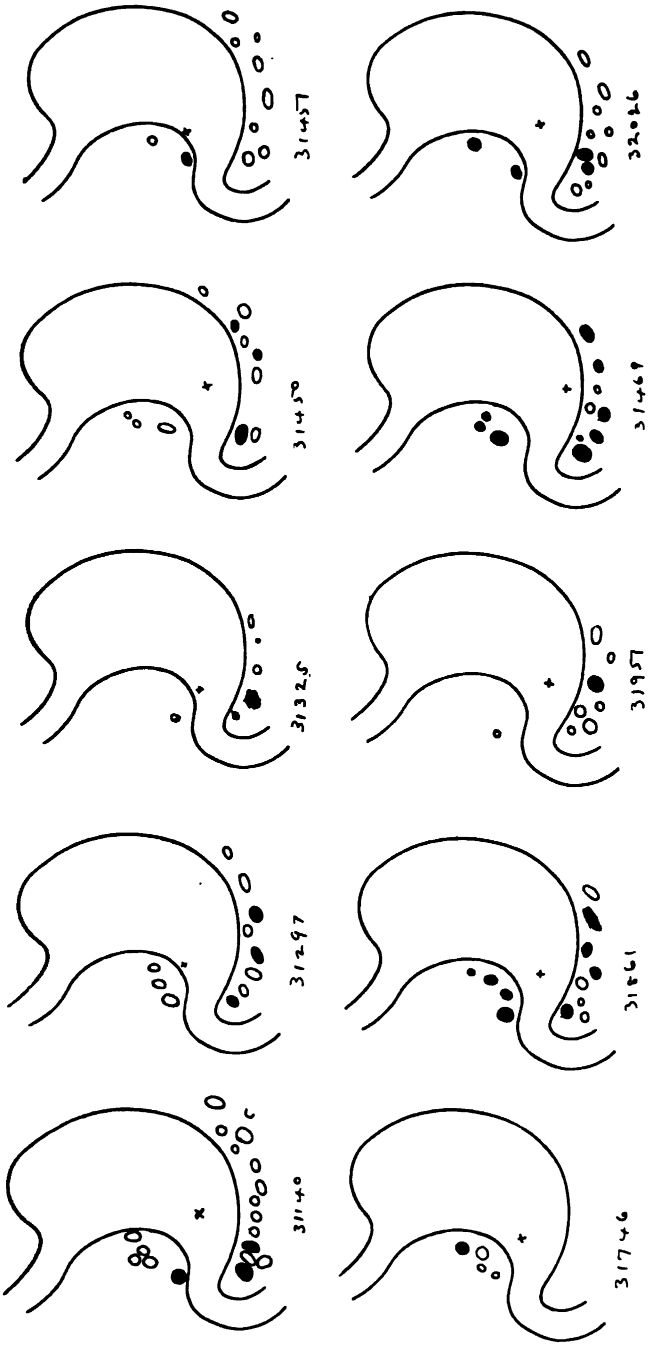


CHART II.—(*Continued.*)

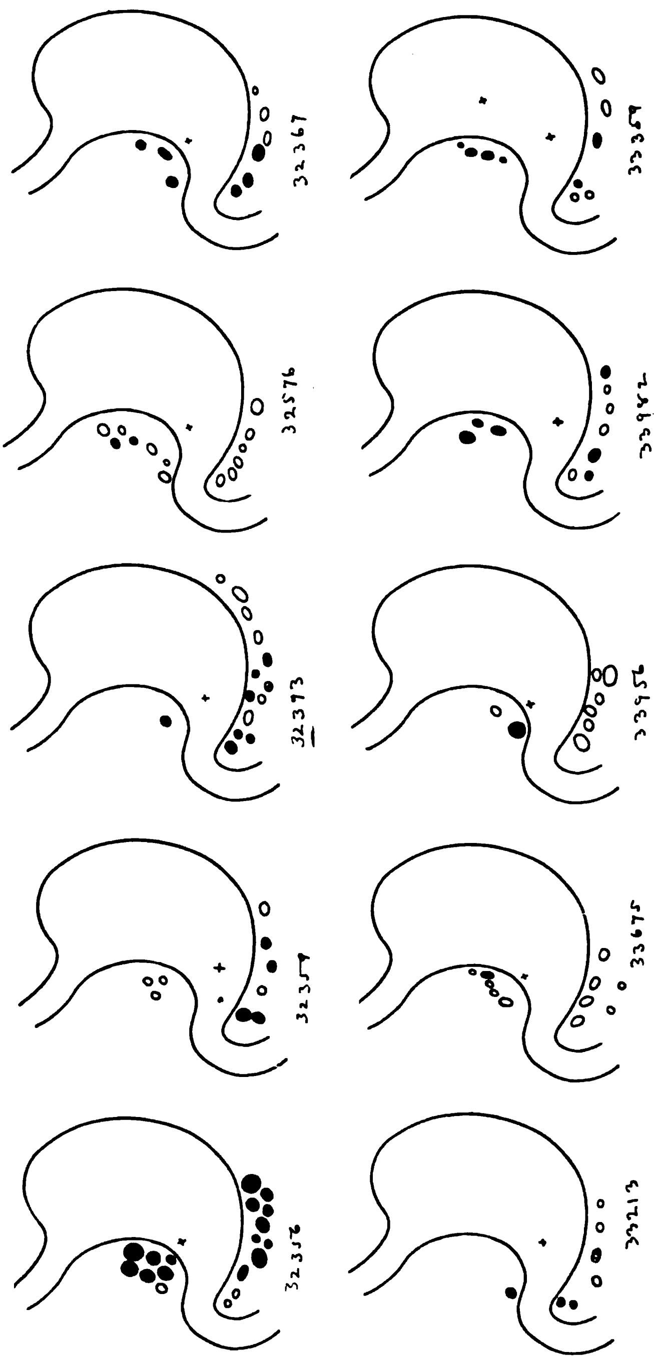


CHART II.—(*Continued.*)

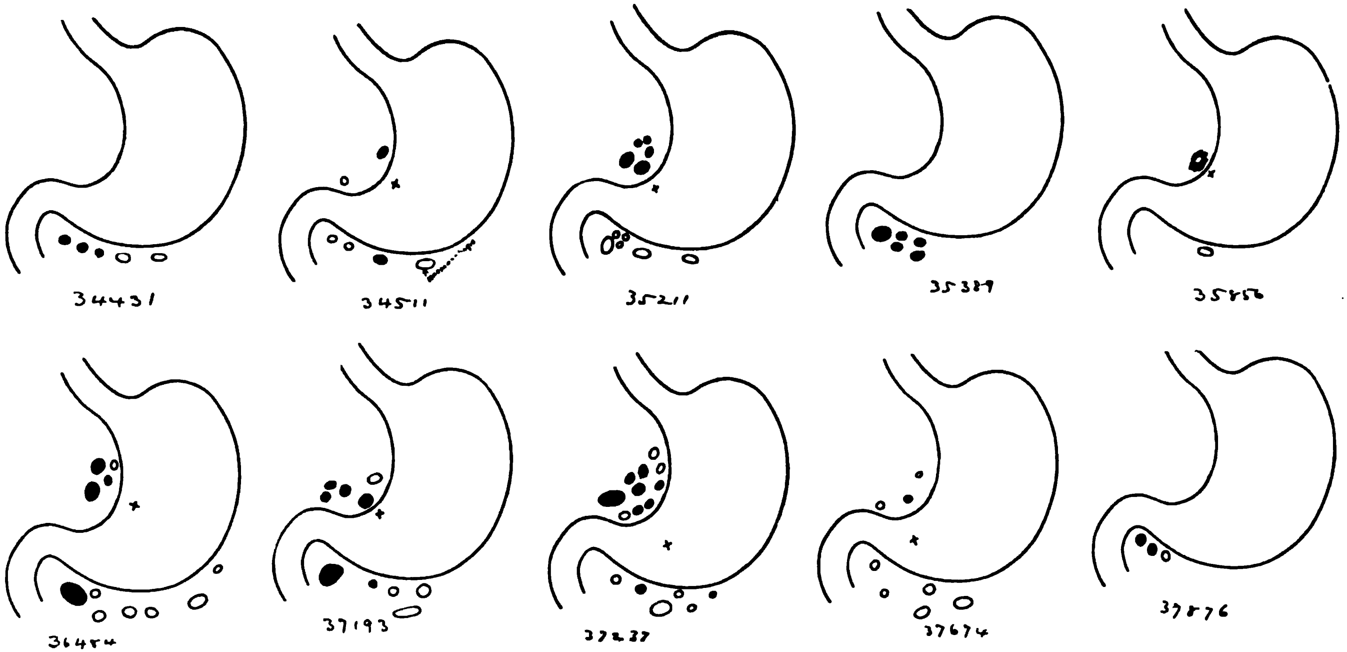


CHART II.– (*Continued.*)

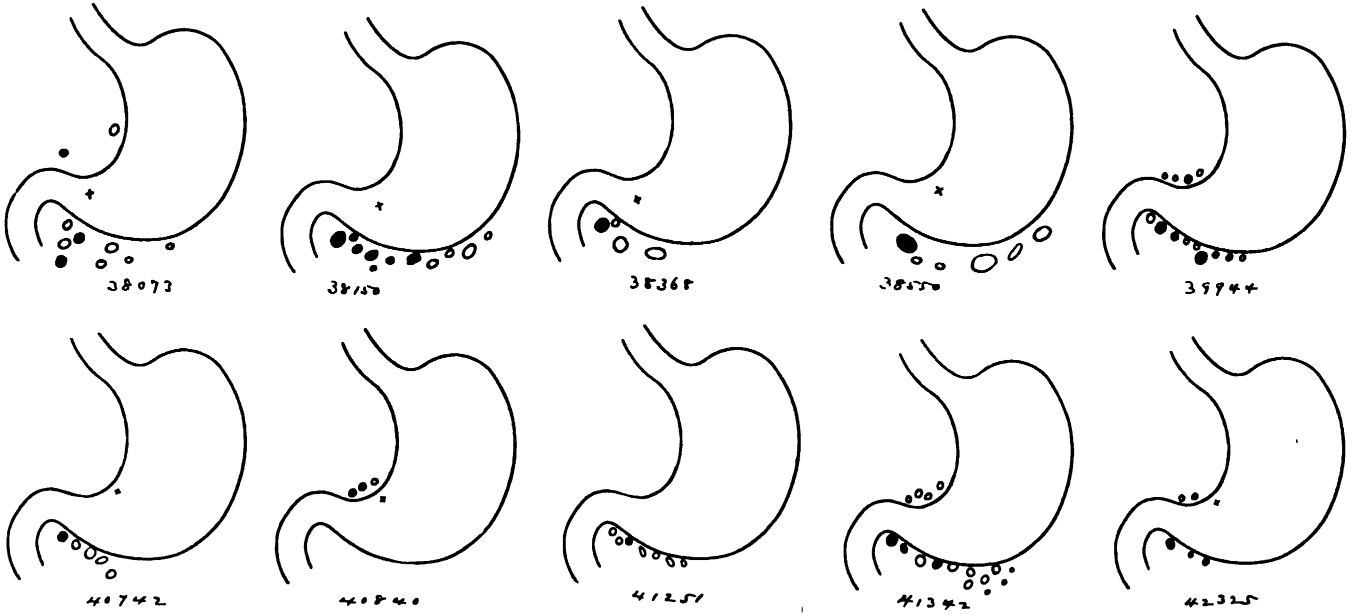


CHART II.—(*Continued.*)

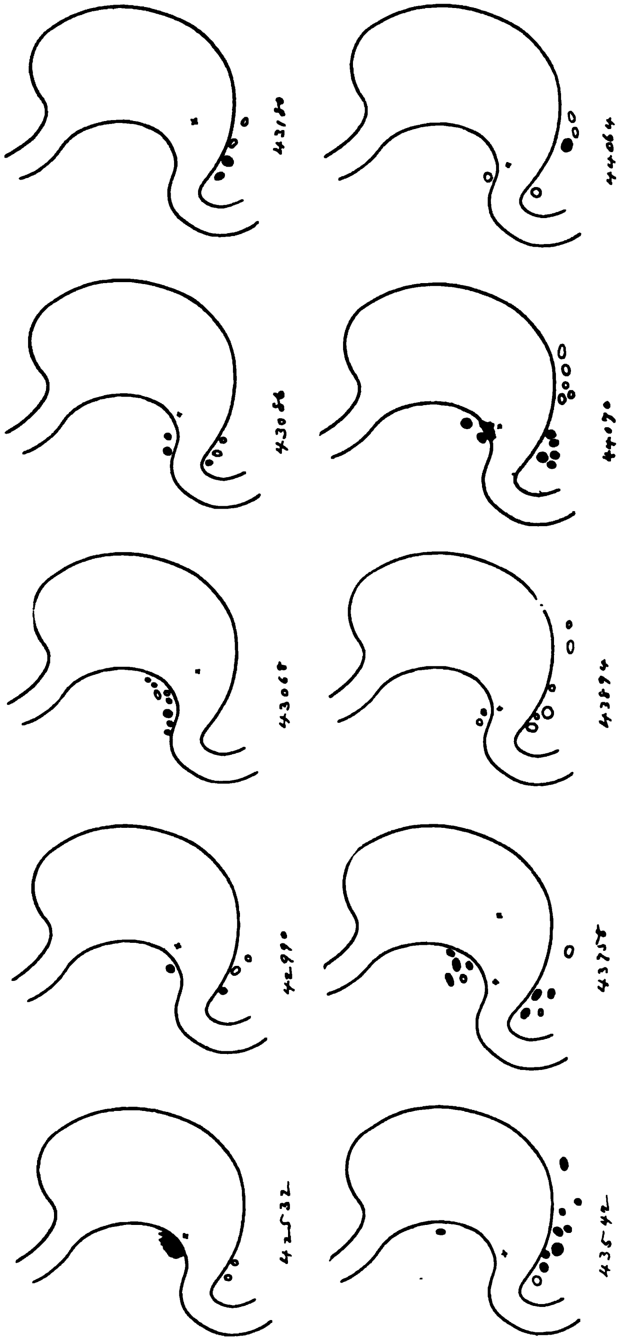


CHART II.—(*Continued.*)

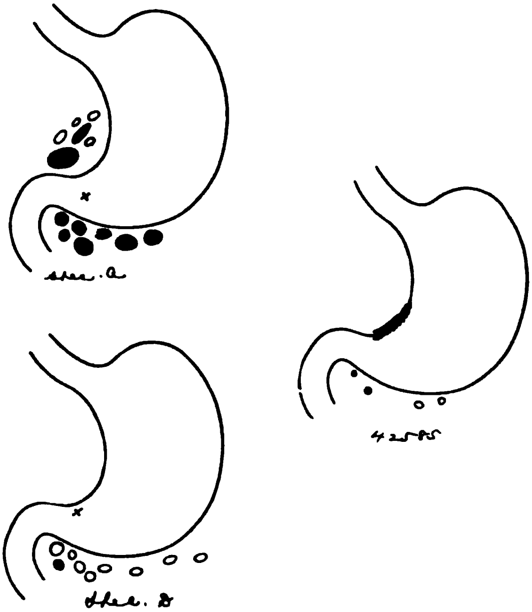


CHART II.—(*Continued.*)

GROUP III

Case No.	Total No. Glands	Total No. Glands Lesser Curvature	Total No. Glands Greater Curvature	Total No. Glands Lesser Curvature Involved	Total No. Glands Greater Curvature Involved	Case No.	Total No. Glands	Total No. Glands Lesser Curvature	Total No. Glands Greater Curvature	Total No. Glands Lesser Curvature Involved	Total No. Glands Greater Curvature Involved
14849	7	4	3	4	3	18466	9	3	6	3	6
14857	11	4	7	4	7	18468	5	2	3	2	3
14897	1	1	0	1	0	18728	4	0	4	0	4
15357	5	3	2	3	2	19574	15	5	10	5	10
15681	4	3	1	3	1	21873	3	0	3	0	3
15775	8	6	2	6	2	21882	3	3	0	3	0
16142	3	1	2	1	2	23025	5	0	5	0	5
16525	13	3	10	3	10	23654	4	1	3	1	3
16636	9	2	7	2	7	27898	3	1	2	1	2
16651	4	2	2	2	2	29402	8	0	8	0	8
16955	2	2	0	2	0	31855	6	1	5	1	5
17377	2	1	1	1	1	33445	21	15	6	15	6
17407	Esophageal glands.					33779	5	3	2	3	2
17715	8	4	4	4	4	40605	1	1	0	1	0
18088	5	2	3	2	3	41070	6	0	6	0	6
18430	5	3	2	3	2	43393	1	1	0	1	0

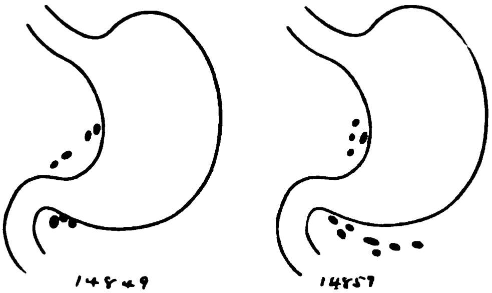


CHART III.—Group III: Diagrams of Specimens with Total Carcinomatous Glandular Involvement. Carcinomatous Glands are Solid Black.

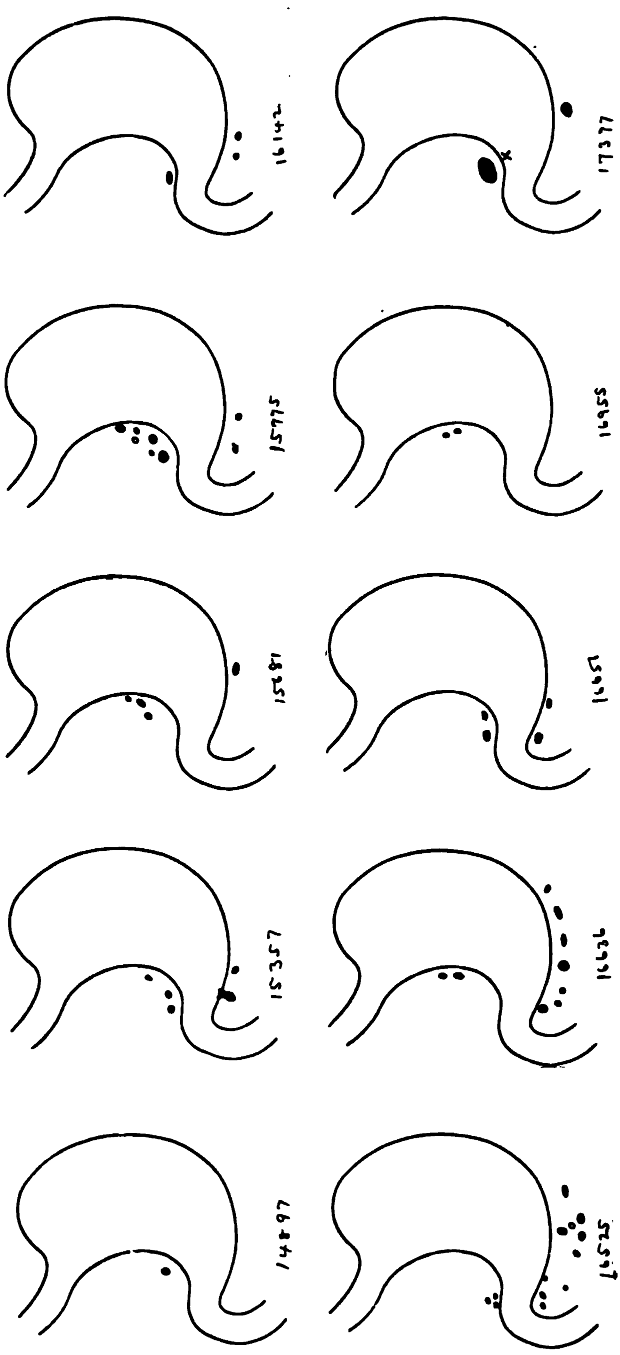


CHART III.—(*Continued.*)

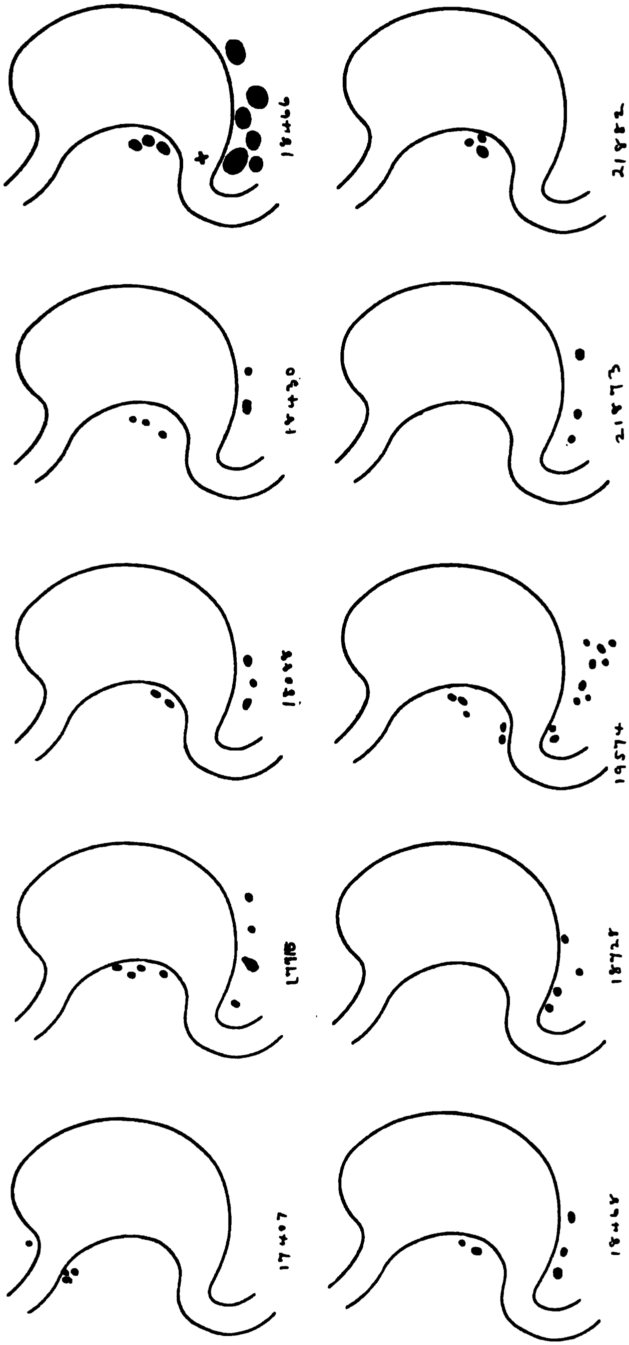


CHART III.—(*Continued.*)

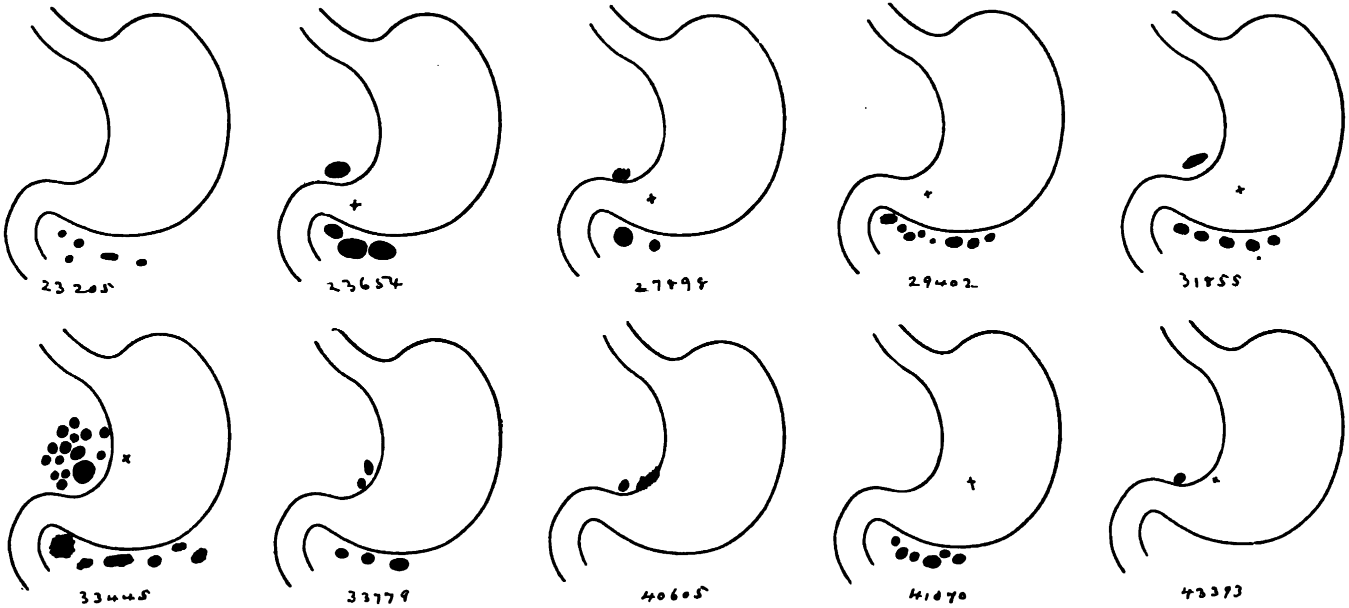


CHART III.—(*Continued.*)

JEJUNOSTOMY*

WILLIAM J. MAYO

Jejunostomy is an operation of considerable usefulness; it gives rest to the stomach and maintains good nutrition. The operation is an active competitor of gastrostomy in cases of esophageal and cardiac obstruction, and in extensive ulcers which cannot be excised and gastrojejunostomy is not feasible it is a most valuable procedure. In malignant diseases of the stomach of the ulcerous type it offers a means of palliation.

The technic of jejunostomy is simple and easily carried out. The abdomen is opened by an epigastric incision either in the midline or to the left in the rectus muscle. The jejunum is picked up and, selecting a point from 12 to 16 inches from its origin, a loop is drawn out of the abdomen, nicked on the convex surface and a No. 9 (English scale) rubber catheter pushed through the opening down stream until it extends about 3 inches inside the lumen of the jejunum (Fig. 10). This point is fixed in position by a single chromic catgut suture; the catheter is then infolded by the jejunal wall for an inch or an inch and a half by mattress sutures of linen, after the plan of Witzel (Fig. 11). The intestine is anchored to the peritoneum by 2 or 3 linen sutures in the lower angle of the incision, which is closed down to the tube in the usual manner (Fig. 12), or the end of the catheter can be brought out of a small stab wound at one side of the incision, the intestine being fixed to the peritoneum on the inside by several linen sutures.

Liquid feeding may be commenced at any time and carried out for an indefinite period without danger of leakage and with a certainty that the nutritive material will pass into the assimilative

---

* Abstracted from the "Amer. Jour. Med. Sci.," April, 1912, pp. 469–473. Copyright, 1912, by Lea and Febiger.

tract. Leakage does not follow the removal of the tube, and if it should slip out accidentally, it must be replaced within twelve hours or the tract may become obliterated. All kinds of fluid nourishment are borne well in these cases—preparations of milk, eggs, meat ground fine and mixed with fluid, carbohydrates in fluid form, etc.

In none of our cases have we observed subsequent ill effects from the jejunum becoming adherent to the peritoneum after the removal of the feeding tube.

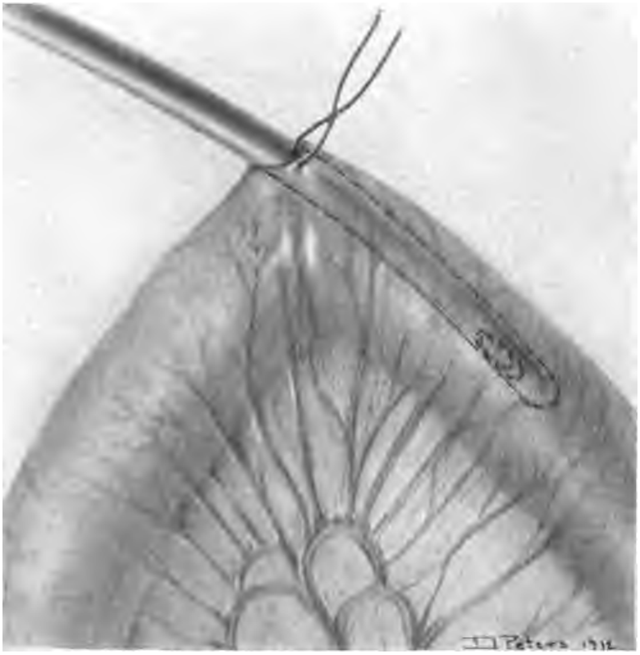


Fig. 10.—Jejunostomy: First step, showing catheter introduced into upper jejunum and fastened with a single suture.

In cases of esophageal and cardiac obstructions, and in diseases affecting a considerable portion of the wall of the stomach, rendering gastrostomy impossible or difficult, jejunostomy is as efficient as, and easier of performance than, gastrostomy. It is in extensive ulceration of the stomach that jejunostomy has its greatest field of usefulness. Sometimes the stomach contains multiple ulcers, either simple or specific, in which temporary rest is indicated, and gastrojejunostomy is impracticable on account of the extent

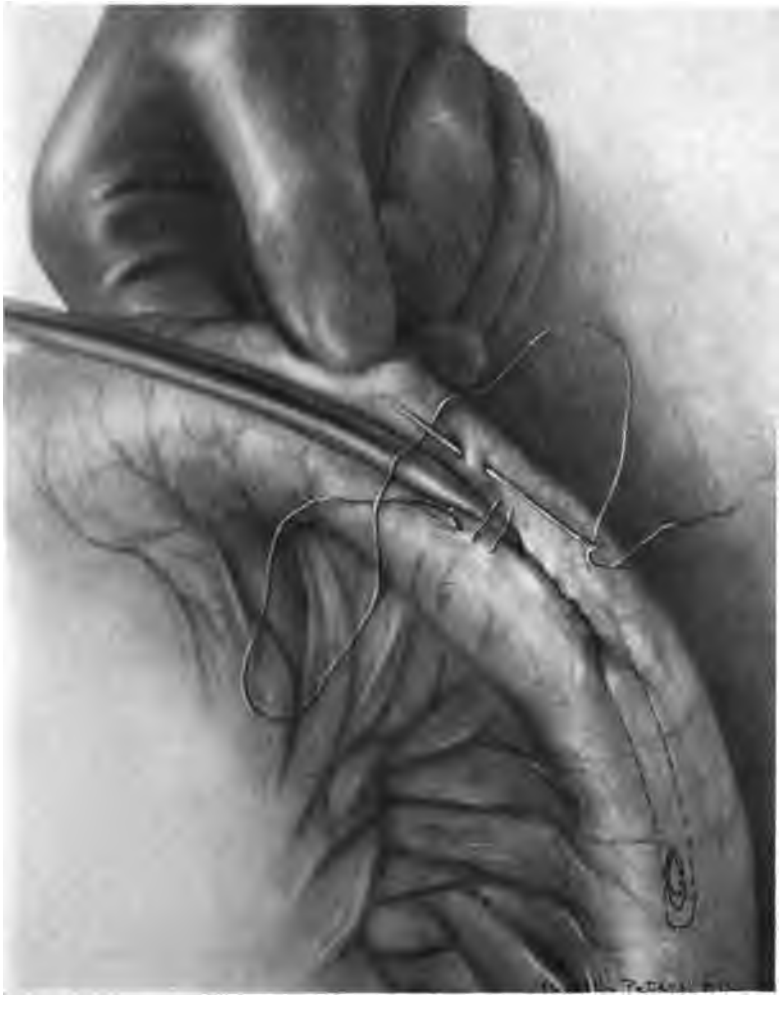


Fig. 11.—Jejunostomy: Second step, showing infolding of catheter.

of the disease. In these cases jejunostomy affords needed rest to the stomach, a condition, it is true, which can be brought about by rectal feeding, but this procedure can in no sense be considered a building-up process; it is useful only as a temporary expedient to prolong life. On the other hand, jejunostomy improves the nutrition of the patient—a gain of from 10 to 30 pounds can easily be made without resorting to forced feeding.

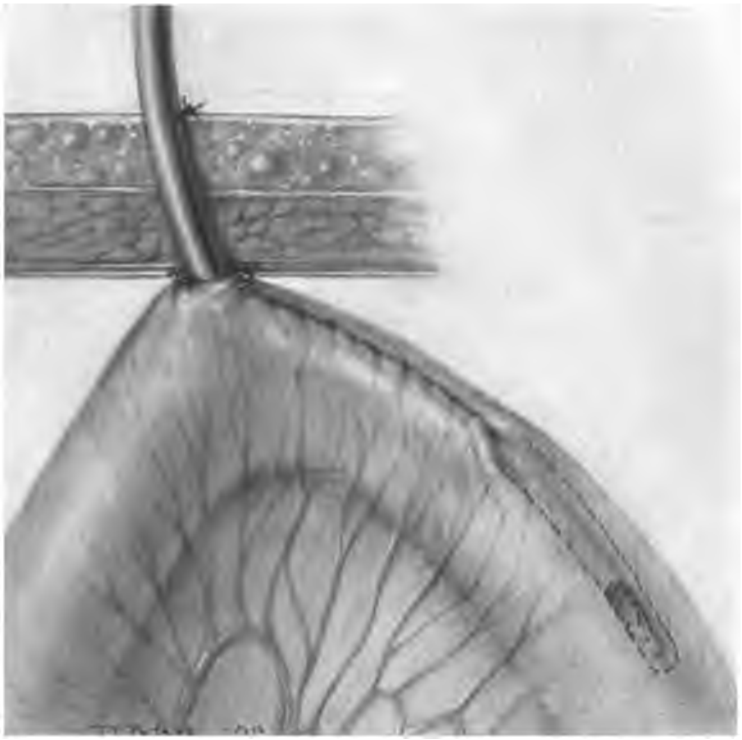


Fig. 12.—Jejunostomy: Third step, operation completed; jejunostomy fastened to abdominal wall.

In this hypernutrition, with rest to the stomach, lies the secret of the remarkable results following jejunostomy in some cases of extensive gastric ulcers. One sometimes finds a large ulcer of the stomach so adherent and extensive, and situated so high in the body, as to render gastrojejunostomy not only hazardous, but open to the serious objection that it must be made distal to the ulcer. In such cases jejunostomy is a rational procedure, and even if the ulcer be malignant in character, the method furnishes a useful means of palliation.

Another indication for jejunostomy is in the treatment of accidental injuries to the cancerous stomach during exploration. Somewhat over a year ago, while exploring a stomach which contained a large ulceration in the vicinity of the pylorus, trying to determine whether it was benign or malignant, I accidentally made a perforation into the foul crater of the ulcer, which proved to be malignant and wholly inoperable. In attempting to repair the injury, complete separation through the cancerous mass occurred. Gastrectomy was out of the question, and the state of the tissue prevented the possibility of closing both ends and doing gastrojejunostomy. I therefore reunited the cancerous tissue as best I could with interrupted chromic catgut sutures, many of them tearing out, as the tissue would not stand the strain. I then formed a sling about the line of union in the stomach with omentum, holding it in place with catgut sutures. A few rubber-tissue drains were placed about the injured stomach, and jejunostomy was performed. The patient was fed two months by this means. There was considerable foul discharge along the drainage tract, which lasted several weeks. The catheter was removed in eight weeks; the patient gained 30 pounds in weight, and lived more than a year without gastric distress and in great comfort. There was no return of obstructive symptoms in this case, although before operation the obstruction was so marked that the patient was in a state of chronic starvation and cachexia. We have observed two similar cases.

It sometimes happens, after the excision of a large ulcer of the stomach, that the organ is not in a safe condition to hold food. This is especially true of large ulcers of the posterior wall. The patients are often so debilitated that improvement in nutrition is almost a necessity in order to obtain union. Jejunostomy furnishes an easy, safe manner of giving the stomach rest during the healing process, the patient is relieved of the danger of leakage, and adequate nourishment is maintained.

I am indebted to Dr. Clairmont, of Vienna, for calling my attention to the value of jejunostomy, and subsequently my interest in the operation was increased by Dr. Frank Billings, who advocated the operation on theoretic grounds—grounds which have proved correct in our clinical experience.

Note.—Since writing the above my attention has been called to an article in the "British Medical Journal," January 6, 1912, by Mr. Mayo Robson, in which he advocates jejunostomy in conditions of the stomach not amenable to other methods of treatment, and gives a résumé of his cases.

OPERATIVE RESULTS IN CARCINOMA OF THE GASTRO-INTESTINAL TRACT*

WILLIAM J. MAYO

Our knowledge of carcinomas of the gastro-intestinal tract is far from being exact, and during the stage of local involvement it is often impossible to determine the presence of malignant disease. A study of the living pathology, as developed through operative procedures and experimental research, has aided greatly to a clearer understanding of existing conditions, and much progress in technic, as applied to radical procedures, has come through a study of embryology and anatomy.

The stomach may be described embryologically and anatomically as a muscular organ, with temporary storage function, and is lined with secreting mucous membrane. It consists of two well-defined compartments: First, the fundus, into which food is immediately received; and, second, the pyloric antrum, where the secretions are most profuse and the muscular action is most powerful.

Phylogenetically, the fundus of the stomach has been a late development, and is consequently more or less under the control of the cerebrospinal nervous system. It follows, therefore, that the derangements of the entire gastro-intestinal tract may reach the consciousness of the individual through the stomach. The control of the intestinal tract, including the antrum of the stomach, is primitive, and is incited by means of internal secretions.

The small intestine is the most primitive part of the gastro-intestinal tract, and it is reasonable to suppose that its longer

---

* Read before the Annual Alumni Meeting of the London Medical College, London, Canada, October, 1912.

OPERATIVE RESULTS IN CARCINOMA OF THE GASTRO-INTESTINAL TRACT*

WILLIAM J. MAYO

Our knowledge of carcinomas of the gastro-intestinal tract is far from being exact, and during the stage of local involvement it is often impossible to determine the presence of malignant disease. A study of the living pathology, as developed through operative procedures and experimental research, has aided greatly to a clearer understanding of existing conditions, and much progress in technic, as applied to radical procedures, has come through a study of embryology and anatomy.

The stomach may be described embryologically and anatomically as a muscular organ, with temporary storage function, and is lined with secreting mucous membrane. It consists of two well-defined compartments: First, the fundus, into which food is immediately received; and, second, the pyloric antrum, where the secretions are most profuse and the muscular action is most powerful.

Phylogenetically, the fundus of the stomach has been a late development, and is consequently more or less under the control of the cerebrospinal nervous system. It follows, therefore, that the derangements of the entire gastro-intestinal tract may reach the consciousness of the individual through the stomach. The control of the intestinal tract, including the antrum of the stomach, is primitive, and is incited by means of internal secretions.

The small intestine is the most primitive part of the gastro-intestinal tract, and it is reasonable to suppose that its longer heredity makes it more resistant to malignancy than the stomach and large intestine, which have developed later.

---

* Read before the Annual Alumni Meeting of the London Medical College, London, Canada, October, 1912.

Embryologically, the large intestine is developed on the left side of the abdomen. The head of the colon begins to rotate at about the eleventh week. As the rotation progresses the colon carries with it the blood-vessels, lymphatics, and nerves, and, when its normal situation is finally reached, the outer layer of mesenteric attachment is merely a peritoneal adhesion, the division of which, at any situation, enables that part of the colon to be turned upon its long inner mesenteric leaf, which contains all the important structures. The costocolic ligament, which holds the splenic flexure in its elevated position, is derived from the omenta and carries a blood-vessel. The elevation of the splenic flexure acts mechanically to detain the food-products in the proximal absorbing half of the colon.

The true rectum lies between the levator ani muscle and the third sacral vertebra, and consists of the so-called second part of the rectum (of American anatomists). It is derived from the cloaca, which is a highly differentiated part of the hindgut, and has 5 sources of blood-supply, all of which may be accompanied by lymphatics. The superior rectal and the middle hemorrhoidal arteries contribute the main blood-supply, however, and the lymphatics, which are scanty, usually pass along with these blood-vessels by way of the rectal, sacral, mesosigmoidal, and the internal iliac glands to the juxta-aortic group.

The rectum proper has no mesentery, and only a small part of its anterior surface is covered by peritoneum. It lies in the fatty supporting tissue inside the rectal fascia, between the genito-urinary organs ventrally and the sacrococcygeal framework dorsally. Carcinomas of the true rectum are covered by peritoneum ventrally to some extent in more than half the cases.

The so-called third portion of the rectum is derived from the ectoderm, or skin fold, and its lymphatics drain into the inguinal and coccygeal glands, as well as upward into the rectal glands. The anal canal is about 1¼ inches in length, contains no glands, and is lined with pavement epithelium. This part is the primary source of malignant disease in about 6 per cent. of the cases of cancer of the rectum.

Taking the gastro-intestinal tract as a whole, we find that the celiac axis supplies those organs derived from the foregut; that is, the stomach, liver, pancreas, and duodenum, down to the common duct. The superior mesenteric artery supplies all those organs which are derived from the midgut, and which are instrumental in assimilation and absorption. They are composed of the duodenum beyond the common duct, the jejunum, ileum, cecum, and ascending and transverse colon as far as the splenic flexure. Ninety per cent. of the solids are picked up in the small intestine, while 50 per cent. of the liquids and 10 per cent. of the solids are absorbed in the cecum and colon proximal to the splenic flexure. The cecum may be described as the stomach of the large intestine; that is, a temporary storehouse from which waste material is passed onward. The cecum, unlike the stomach, is actively engaged in absorption. It is possible that in the attempt to conserve food from waste under septic conditions toxic products are here often taken up, to the serious detriment of the individual.

The inferior mesenteric artery supplies the derivatives of the hindgut, and the normal movement, except during defecation, is antiperistaltic. By means of mucous currents the distal colon is intermittently engaged in passing material for further elaboration and assimilation backward into the area of midgut absorption. Under normal conditions the contents of the large intestine, as far as the splenic flexure, are fluid or semisolid. The descending colon is usually empty, acting as a passageway only into the sigmoid, where the feces become more solid in character.

Tumors of the cecum and colon proximal to the splenic flexure are sometimes accompanied by changes in metabolism; the nutrition of the patient often suffers, and profound anemia may result. Tumors of the descending colon and sigmoid are seldom accompanied by changes in nutrition, and it is the mechanic effect of the tumor, usually an attack of obstruction, which first calls attention to the patient's condition.

The relation of irritation to the development of carcinomas of the skin is generally recognized, but this relationship has not been associated with carcinomas of the gastro-intestinal tract. In about 50 per cent. of the resections for cancer of the stomach performed in our clinic cancer was found to have developed on ulcer, and in nearly 20 per cent. of resections for cancer of the sigmoid we found it to have developed on diverticula.

The physiologic function of the lymphatics is a most important factor in relation to the radical cure of carcinomas. The proof of this assertion cannot be better shown than in the results after resection of the various organs of the gastro-intestinal tract.

The stomach is generously supplied with lymphatics, and gives the smallest percentage of radical cures. The larger part, composed of the dome and fundus, has but a scanty supply of lymphatics, which pass to the left to the glands lying in the splenic area, and to the cardiac glands about the esophagus. The smaller pyloric segment has nine-tenths of all the lymphatics of the stomach. They are divided into four groups: (1) The lymphatics lying in the wall of the stomach along the lesser curvature, and draining into the glands about the celiac axis. (2) Those along the greater curvature, which lie beside the gastro-epiploic vessels. In this region the lymphatic current passes from left to right toward the pylorus. (3) The important group lying about the pylorus, the first portion of the duodenum, and the head of the pancreas, and draining into the glands inferior to the pylorus. (4) The few lymphatics which pass with the superior pyloric vessels.

The situation of these four groups of lymphatics is definitely determined by the four accompanying blood-vessels, so that early ligation of the gastric, gastroduodenal, superior pyloric, and gastro-epiploic vessels not only permits bloodless operation, but enables radical removal of the associated lymphatics. Unfortunately, this lymphatic arrangement may be disturbed, first, because of the fact that the lymphatic drainage may be irregular, passing by some glands and emptying into more distant ones; or, second, by blocking of a main lymphatic trunk the lymph flow may be turned into by-paths leading into the preaortic glands. When the disease is advanced, both of these conditions may be found to exist.

The small intestine has a larger number of lymphatics than the large intestine, but, fortunately, is seldom affected with carcinoma.

The large intestine has the least supply of lymphatics, and gives the highest percentage of radical cures following operation for carcinoma. They lie beside the blood-vessels, and, usually, are easily removed. Many times microscopic examination of enlarged lymphatic glands will show the enlargement to be the result of infection, and not a carcinomatous growth.

The rectum, with a moderate supply of lymphatics, gives better operative results than the stomach, but less favorable than the large intestine.

Of the 1498 operations for carcinoma of the gastro-intestinal tract which were performed in St. Mary's Hospital from October 1, 1897, to October 1, 1912, 996 involved the stomach, 16 the small intestine, 216 the large intestine, and 225 the rectum. It will be noted that in this series more than two-thirds of the carcinomas occurred in the stomach.

Cancer, as cancer in the stomach, does not produce symptoms upon which an early diagnosis can be made. Only when its situation makes a palpable tumor mass or produces obstruction can a probable diagnosis be established.

The mortality following resections of the stomach is steadily diminishing. It is now from 7 to 10 per cent., and depends more upon the patient's condition at the time of operation than upon the operation itself. Taking into consideration that the initial recoveries are in the vicinity of 90 per cent., and that these patients are given a chance of permanent cure approximating 25 per cent., it seems incumbent upon the medical profession to make a more determined effort toward an early diagnosis.

In our series of 996 cases of carcinoma of the stomach it was possible to do the radical operation in only 344, or 34.5 per cent.

Five of the 16 cases of cancer of the small intestine reported in this series were in the duodenum, and none of them was operable. In 2 cases the duodenojejunal angle was involved, and both were inoperable. Of the remaining 9 cases, 4 involved the jejunum and 5 the ileum. In 2 of the 5 cases submitted to excision the disease had begun in a pedunculated adenoma or papilloma, and intussusception was present.

In operating for carcinomas of the large intestine it sometimes happens that one or more loops of the small intestine may have become adherent and involved secondarily with the tumor mass. As a rule, this takes place along the periphery of the small bowel. On a number of occasions we have resected a loop of the small intestine; twice we have removed two separate loops, and in one instance three loops, removing the primary growth in the colon with the portions of small intestine attached. In 4 cases we removed a portion of the bladder, and in 3 cases the uterus was coincidentally removed. The ultimate results in these cases of multiple resections have been surprisingly good, and we have several such patients alive and well more than five years.

Generally speaking, malignant disease in any part of the large intestine proximal to the middle of the transverse colon is treated best by removal of all the large intestine up to and including the growth, doing an ileocolostomy. Beyond this point resection in continuity, either in one or two stages, is to be preferred. If obstruction is or has recently been present, the two-stage operation is much safer. Forty per cent. of the patients in this group who were operated on radically more than five years ago are alive and well.

The diagnosis of cancer of the rectum is so easy that one wonders why so many patients come for consultation without a diagnosis, and why nearly 15 per cent. of them have been operated on recently for supposed hemorrhoids. It is a simple matter to examine the rectum digitally, and it requires but little skill to use a proctoscope or sigmoidoscope. Neglect of these simple methods of examination causes not only disaster to the patient, but injury to the practitioner's reputation.

Radical operations for carcinoma of the rectum have been hitherto in bad repute. This has been due more to inefficient methods and purely sentimental attempts to conserve function than to the character and location of the disease. In many cases of carcinoma of the rectum a permanent colostomy in the left rectus muscle should be made as the primary operation. At a second operation, after the lower segment has been properly cleansed, the entire rectum should be removed from behind, using a modification of the Kraske technic. The fourth and fifth sacral vertebræ and the coccyx are removed, and a clean dissection is made of the entire rectum, with the fat and glands.

In cases in which the two-stage operation is not advisable the abdominal exploration and permanent colostomy may be omitted, and the posterior one-stage operation with a sacral anus made. In some cases of anemic women the Quénu-Tuttle one-stage perineal operation will be found safe and satisfactory. For carcinomas of the anal canal the Cripps operation of perineal amputation is very satisfactory. In these cases the rectum is not pulled down, but the space is allowed to fill by granulation. High rectal and rectosigmoidal growths will often be approached best through the abdomen, or by the combined method. The frequency with which secondary carcinomas of the liver, peritoneum, or inoperable lymphatic glandular involvement occur makes it advisable in most cases of carcinomas of the rectum and rectosigmoid first to open and explore thoroughly the abdomen, to see if the case is one which should be submitted to operation. In a limited number of favorable cases of cancer of the rectum and rectosigmoid the musculature of the anal canal may be saved and the end of the sigmoid drawn down and attached to the anal outlet, or a direct union can be made in continuity between sigmoid and lower rectum by the tube method.

About 30 per cent. of those patients submitted to radical operation for carcinoma of the rectum more than five years ago, and who recovered from the operation, are alive and well.

Taken as a whole, these statistics indicate that carcinomas of the gastro-intestinal tract which are sufficiently localized to justify radical operation give results fully as good as carcinoma in other parts of the body. The pessimism of the medical profession regarding malignant disease of the gastro-intestinal tract is not justified by the facts. It is the failure to make a diagnosis during the stage when the disease is still localized, and not any peculiar malignant tendencies of the process itself, which accounts for the high mortality of cancer in this region.

SOME OF THE DISPUTED PROBLEMS ASSOCIATED WITH SURGERY OF THE LARGE INTESTINE*

WILLIAM J. MAYO

Much can be learned concerning the underlying causes of diseases of the large intestine by studying the changes which have been incident to the development of its function. In the adult human the large intestine appears as a continuous whole, yet functionally it is sharply delimited at the point of vascular anastomosis between the derivatives of the superior and inferior mesenteric vessels at the splenic flexure. The first half of the large intestine is derived from the same embryologic sources as is the small intestine, and has a similar important metabolic function. About 50 per cent. of the fluids and 10 per cent. of the solids are absorbed in this part of the large intestine. Beyond the splenic flexure absorption is limited in amount, the bulk of absorbable material placed in the rectum being promptly passed into the proximal colon for absorption.

It has been shown by Bond,[1] Cannon,[2] and others that there is a fairly constant antiperistalsis in the large intestine, which passes material back toward the cecum.

The study of comparative anatomy in the herbivorous animal demonstrates the enormous absorptive value of the cecum. Lyle[3] has aptly compared its storage function to the stomach. Unlike the stomach, which absorbs but a small amount, the cecum absorbs actively. In some animals there is a sphincter in the ascending colon to hold the material in the cecum. In man a marked physiologic activity is shown at this point, although no colic sphincter exists.

---

* Reprinted from "Amer. Jour. Med. Sci.," February, 1913, pp. 157-161. Copyright, 1913, by Lea and Febiger.

The portion of the duodenum which lies between the pylorus and the opening of the common duct may be said to be the vestibule of the small intestine, the food passing rapidly through to reach the area of absorption. In a general way the same conditions exist in the descending colon, which also acts as a vestibule through which food refuse passes rapidly to reach the storage chamber of the sigmoid. The splenic flexure of the colon is held high, as a mechanic means of maintaining food-products as long as possible in the first half of the large intestine. This method of retention is more economic in its operation than a muscular sphincter apparatus would be. Some sixty years ago Rokitansky[4] called attention to the fact that the descending colon was usually found empty at autopsy, just as the x-ray bismuth picture today so often shows it in the living, and which is so often misinterpreted as evidences of supposed stricture.

In an article written in 1900[5] I called attention to a contraction of the ileocecal orifice as a cause of certain intestinal phenomena, and pointed out that many cases of constipation might have their origin in metabolic changes in the small intestine rather than in the large. This helps to explain the obstinate constipation which sometimes continues after an ileosigmoidostomy, although such stasis is largely due to the fact that the material from the ileum as it enters the sigmoid passes backward by an antiperistalsis into the first half of the large intestine, and then pursues its ordinary course much as though ileosigmoidostomy had not been done. This has been demonstrated in the x-ray findings following ileosigmoidoscopy in some of our cases.

The sigmoid varies greatly in its length, size, and position, because it is a late development without fixed characteristics (Finney[6]). This is further shown in the weakness of its walls, which in the middle and later decads of life so frequently permit hernias of the mucosa through the musculature. These hernias or diverticula are an important factor in the causation of localized peritonitis from diverticulitis, as well as occasionally the chronic irritating focus in initiating cancer of the sigmoid.

The rectosigmoid juncture is at the third sacral vertebra, and here nature has again introduced certain mechanic obstacles to prevent the too ready discharge from the storehouse of the sigmoid into the rectum. So often a well-trained nurse asks, "Shall I give a high injection with the colonic tube into the colon or a low rectal?" The result, of course, is quite the same. The colonic tube pushed through the anus out of sight lies coiled in the rectum when it is supposed to be in the colon. Such a tube cannot often be made to pass through the rectosigmoid in this manner.

The rectum is not normally a fecal storehouse, although through habit it often becomes so, especially in the female. Examination of the male for service in the army shows the rectum to be empty normally.

Bands of adhesions are often developed during adult life. At the time of birth the cavity of the omentum is obliterated as high as the transverse colon. The process continues until in adult life points of adhesion are found as high as the pyloric end of the stomach, which obliterate the lesser cavity of the peritoneum to a greater or less degree. Similar conditions may exist between the omenta and the gall-bladder, and may be taken as evidence of infection. Various observers have asserted that the adhesions which sometimes exist between the epiploic tags of the sigmoid and the abdominal wall, etc., are of great importance, and always the result of pathologic conditions, yet such adhesions will be found in a certain percentage of necropsies on subjects over forty years of age, who during life showed no symptoms ascribable thereto.

Jackson[7] has called attention to the veil of adhesions so often present between the ascending colon and the abdominal wall as a cause of pathologic symptoms. We can at least say safely that this condition, like the others mentioned, is developmental in origin. The cecum does not reach its normal situation until about the time of birth, therefore the attachment between this late arrival and its fixed place of abode is recent, and resembles adhesions of a peculiar pannus type. The weakness of this attachment on the right side is partially instrumental in permitting the prolapse of the cecum into the pelvis. Wilms[8] believes this prolapse to be of great pathologic significance in producing cecal stasis. "Lane's kink" is undoubtedly also of developmental origin, and due to a fixation by bands of the terminal 3 inches of the ileum. The important question is, Do these conditions produce symptoms, or are they merely anatomic deviations without pathologic meaning?

The transverse colon averages in length from 20 to 22 inches, and has 10 or 11 inches distance to travel from the hepatic to the splenic flexures. Its supporting attachments in the center are to the movable stomach, therefore prolapse of the transverse colon is common. There is little else it can do. The length of the transverse colon serves a physiologic purpose in picking up the final remnants of nutritive material. The *x*-ray photograph, taken with the patient in the standing position, with the weight of the bismuth in the stomach or in the transverse colon, or both, produces an exaggeration of this normal condition. How often can we say that it is truly pathologic?

If the small bands of adhesions which are found in one case, such as a sigmoid epiploic tag attachment to the abdominal wall, be productive of so much harm in one patient, how can we expect that another patient with similar symptoms will be benefited by the bands of adhesions which the surgeon purposely forms to hold up a prolapsed organ like the cecum? How much of truth and how much of fancy are embodied in the elucidation of this subject no one can say. That it is most obscure we all agree. One group of observers is convinced that the whole thing is mechanic, and the result of some type of infection rather than an error of development. Another group contents itself with the belief that these patients are all neurasthenics, although they are less ready to give an opinion as to the cause or nature of the condition. That many of the patients operated on have been greatly benefited cannot be denied, yet if one were to take the case histories and reports of successful treatment by means of such mechanic therapy and put them all in a hat to be picked out at random, one could not determine from the histories of the patients those who had been relieved of symptoms by operating for a mobile cecum, for relief of the adhesions, for mobility of the sigmoid, for fixation of the sigmoid, for prolapse of the stomach, and, for that matter, for movable kidney. The histories read alike, but the operations seem to vary with the bias of the operator. Are all these deductions wrong? Has the profession in regular medicine, with its accurate observations, no conclusions which depend upon more authentic data? To say that relief of symptoms demonstrates the truth of the opinion is not sufficient unless we grant the same privilege to the mental healers.

I think we can agree with Arbuthnot Lane that metabolic changes may take place in the large intestine, which in some cases produce symptoms of disease, and that absorbable toxic products are responsible for many of the symptoms which are spoken of in a general way as gastro-intestinal neurosis, intestinal toxemia, intestinal stasis, putrefactive intoxication, etc.

It is probable that the first part of the colon, and especially the cecum and ascending colon, will be found at fault. To it is delegated the difficult function of culling out the last nutritive remnants from the now infected mass of food. Carcinomas of the cecum and ascending colon are often accompanied by the most profound anemia in cases without glandular or general metastasis. We not infrequently see a removable tumor and a perfect cure follow an operation upon a patient so anemic that the hemoglobin runs as low as 30 and the reds are in the vicinity of 2,500,000. Many such patients have been left to die because this specific anemia was believed to be a cachexia from hopeless malignant metastasis. This same anemia may accompany tuberculous tumor of the cecum of the hypertrophic variety, without ulceration to explain it, but is not found to accompany tumors of the sigmoid, even though there may be sloughing.

It is possible that all these mechanic conditions have some effect in detaining the infected remnants of food too long in the absorbing half of the colon, the symptoms being due to the effect of the toxic products absorbed on the controlling sympathetic ganglia. That the theory of mechanic causation alone is insufficient explanation is established by the fact that, as a rule, none of the ordinary results of mechanic obstruction exist, such as muscular hypertrophy of the wall of the bowel, etc. Quite the opposite condition exists—the bowel is thin walled and ballooned, the patients showing marked evidence of loss of sympathetic balance of the neurasthenic type, resembling in some respects a mild Graves' disease from hyperthyroidism.

The views of Arbuthnot Lane,[9] Rovsing,[10] Coffey,[11] Jackson, and others should receive careful consideration. Whether or not the particular operations advocated by these surgeons are ultimately found to be correct, at least their work has called the attention of the profession to an important and heretofore neglected field, and offers a possible explanation of the cause of the protean symptoms in a large group of patients who have received much treatment and little benefit from the medical profession, and who have been exploited by the dietetic faddist and the charlatan.

REFERENCES

1. Bond: "Med. Rec.," August 12, 1905, pp. 246–252.
2. Cannon: "Amer. Jour. Phys.," 1898, vol. i, p. 359.
3. Lyle: "Brit. Med. Jour.," 1906, vol. ii, p. 238.
4. Rokitansky: "Handbuch der spec. path. Anat.," 1842.
5. Mayo: "Annals of Surg.," September, 1900.
6. Finney: "Trans. Amer. Surg. Assoc.," 1908, vol. xxvi, pp. 475–516.
7. Jackson: "Surg., Gyn. and Obst.," 1909, vol. ix, pp. 278–287.
8. Wilms: "Arch. d. klin. Chir.," 1903, vol. lxix, pp. 795–842.
9. Lane: "Surg. Gyn. and Obst.," February, 1908, p. 115.
10. Rovsing: "Samml. klin. Vort.," 1906, vol. xv, No. 431.
11. Coffey: "Annals of Surg.," January, 1907, pp. 43–49.

THE DIAGNOSIS OF DIVERTICULITIS OF THE LARGE BOWEL

A CLINICAL REVIEW OF 27 CASES*

H. Z. GIFFIN

Our earlier experience at St. Mary's Hospital with diverticulitis of the large bowel has been reported in former articles.[1] The clinical similarity of diverticulitis and carcinoma has been emphasized. The condition has been placed clearly on a definite pathologic basis, and the possibility of the development of carcinoma on diverticulitis has been demonstrated. A more detailed analysis of the symptoms and the physical findings in a group of personally observed cases has not, however, been made, and it is with the idea of determining whether or not a more or less definite clinical picture presents itself that this review is undertaken.

From January 1, 1902, to January 1, 1912, 27 operations for diverticulitis of the large bowel were performed in the Mayo Clinic, and the cases were studied clinically and pathologically. This number includes only those cases in which the operation was done primarily for this condition. One of them has been previously reported by Graves,[2] and 8 by my associates and myself.[1] The entire group has been reviewed from an anatomic standpoint by McGrath,[3] and the reader is referred to his paper for the details of the pathologic diagnosis. In 4 additional cases diverticula with slight pathologic change were found as a secondary condition, and in one other case an anastomosis was made subsequent to a resection for diverticulitis of the sigmoid elsewhere.

---

* Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-third Annual Session, held at Atlantic City, June, 1912. Reprinted from the "Jour. Amer. Med. Assoc.," September 14, 1912, vol. lix, pp. 864–866.

Moreover, in 7 instances a condition suggesting diverticulitis was found at operation, but diverticula could not be demonstrated positively. In all, then, 39 cases have been observed which were either positively proved to be diverticulitis or in which this condition was strongly suspected at operation.

Of the 27 cases which came directly under our consideration, 22 were in the sigmoid or the sigmoid and descending colon, while 2 occurred in the rectum, 1 in the transverse colon near the hepatic flexure, 1 at the hepatic flexure, and 1 at the anal ring. Carcinomatous degeneration had taken place in 5 of the 22 specimens from the sigmoid. The remaining 17 cases of simple inflammatory lesion occurring in the sigmoid constitute the most important group for a consideration of the clinical manifestations which may differentiate the condition and assist us in arriving at a clinical diagnosis, and these will, therefore, be considered first. During the same period of time there were 120 operations for carcinoma of the sigmoid. The relative frequency of diverticulitis and carcinoma is, therefore, as 1 is to 7.

Symptomatology in Non-malignant Lesion of the Sigmoid

Preoperative Diagnoses.—Only 3 of the 17 cases were diagnosed as carcinoma. From a clinical standpoint it was thought that the rest might be inflammatory. One was diagnosed as acute appendicitis; in this case the appendix was in reality inflamed, but the abscess was secondary to a perforating diverticulitis of the sigmoid. Four of the patients, all women, presented pelvic tumors, and these were in every instance believed to be inflammatory clinically. In them bowel symptoms were absent except for severe constipation, which is so common a complaint in women, especially with pelvic disease. Two cases were diagnosed simply as "tumors of the sigmoid," and this implied a doubt as to their malignancy. In 7 instances diverticulitis was recorded in the clinical history as the diagnosis of preference, though it is true that in one of these the diagnosis had been made pathologically at a former operation elsewhere. The point for emphasis, however, is this: that there must have been something in the clinical picture which in all cases save 3 led the physician to doubt in some measure the existence of malignancy.

Age.—In this group of 17 the youngest patient was forty years of age and the oldest seventy-three. The average age was a little less than fifty-four years. There were 5 between forty and forty-nine years; 8 between fifty and fifty-nine; 3 between sixty and sixty-nine, and 1 was over seventy. The time of greatest frequency was from forty-five to sixty years, 9, or more than half, occurring in this period.

Sex.—Five patients were females and 12 males.

Occupation.—This is of fraternal interest only in that 3 of the patients were surgeons.

Weight.—In general, the type of patient was uniform. An inclination to at least an "enviable" obesity was noted. Even though the patients were neither tall nor heavy, the ratio of weight to height was increased. In 7 instances the weight was accurately noted and its average was 180 pounds. Three more were described stout. Only one patient weighed less than 150 pounds, and, though short of stature, was not lacking in a suggestion of abdominal rotundity.

Nutrition.—In all but 3 instances the nutrition was noted. It was either good or excellent. This means that the patients were well nourished and of sound flesh and good color. The loss of weight varied from 5 to 30 pounds, and averaged less than 10 pounds, and those showing marked loss of weight were originally very heavy.

Pain.—Fourteen of the 17 patients gave a history of abdominal pain of considerable severity, 2 of very slight pain, and 1 of a sense of uneasiness, distress, and gas in the region of the navel and across the lower abdomen. In 8 the pain was crampy in character and of varying severity; in 7 it was spoken of as an ache, and differently described as dull or deep, or as a distress or pressure, while in 2 tenderness only was complained of. Nine, or a majority of the patients, gave a history of very definite localization to the course of the descending colon and sigmoid flexure at various times. In 8 of the cases, however, the pain was never thought by the patient to localize itself definitely in the left lower quadrant, but was referred to the lower abdomen, though examination invariably demonstrated that the tenderness was definitely in the left iliac fossa. All of the females, 5 in number, and 2 males gave a history of pelvic pain also. In these 7 the mass was found to be adherent in the pelvis, and in 1 it was partially intussuscepted into the rectum.

The total duration of abdominal pain varied from twenty days to five, eight, and twelve years. In this great variability in the length of the history of pain the condition resembles other inflammatory lesions of the abdomen. In 10, or a majority of the cases, the total duration of abdominal pain was longer than one year. In 2 it was less than one month; in 5, less than a year.

In 10 instances attacks of low abdominal colic had occurred and were of moderate severity in all but 2; in these they were extreme. Seven had had no attacks, and the complaint was of a more nearly constant character. In those cases having attacks of pain the duration of the attack varied from a few hours to a few days, most of them lasting from two to four days.

In 8 instances a history of abdominal pain preceded the discovery of a mass by periods varying from three months to twelve years. In 5 of these the period was longer than one year, and in 4 longer than two years. If it can be determined with a reasonable amount of certainty that there is a long history of abdominal pain, especially occurring in attacks and with definite localization, this may be regarded as evidence in favor of a diagnosis of inflammatory lesion. If, in addition to this, there is a history of the previous formation of a mass and its subsequent disappearance, the diagnosis is strongly confirmed. One of our patients gave a history of having noted a mass with an attack eight years previously and this had disappeared.

Vomiting, Diarrhea, and Constipation.—Vomiting was not an important symptom. It occurred in 3 cases during attacks of colicky pain. Similarly, diarrhea was noted twice, and then for a few days only at any one time. Constipation was complained of in a majority of the cases, and was of more than moderate severity in 9 of the 17. In 8 of these it seemed to amount to a chronic obstruction from the clinical standpoint. Pathologically, 8 showed evidence of moderate or marked narrowing of the bowel; 5 a slight narrowing. No case of acute obstruction was seen.

Manual Examination.—In all cases a mass could be felt in the left lower quadrant or in the pelvis. In males the bimanual examination by rectum enables one to obtain a very clear idea of the size and outlines of the tumor. In women the left pelvic mass was a constant finding, and in one case it was adherent low in the culdesac.

Blood Count and Temperature.—Leukocytosis might be considered as evidence in favor of diverticulitis. In 3 cases only was the leukocyte count recorded. It was 13,000, 14,000, and 20,000. In 8 cases a reasonably accurate estimate of the fever during attacks of abdominal pain could be obtained from the patient. It varied from 99.5 to 104.

Bladder Examination.—In 3 instances only were vesical symptoms noted. One patient had complained of frequency and tenesmus for two years. Feces and gas had been passed by urethra for one year. The cystoscopic examination revealed two fistulas in the roof of the bladder, which, from their appearance, seemed to be inflammatory. They were neither rigid nor indurated. This evidence helped materially in making a correct diagnosis of the condition. The other two patients complained merely of difficulty in starting the flow or of imperfect control.

Rectal Examination.—The proctoscopic examination was negative in all cases of simple inflammatory lesion save one, in which the tumor had become partially intussuscepted into the rectum. The instrument was inserted from 6 to 15 inches in 7 of the cases. The fact that pathologically there is no ulceration within the bowel in most of the specimens makes it unlikely that definite changes can be recognized even when one is able to insert the proctoscope sufficiently far. *X*-ray plates of the colon after the injection of bismuth from below were negative in 2 cases.

Blood in the Stools.—A fact of the greatest importance in the differentiation of diverticulitis of the sigmoid from carcinoma seems to be a history of the absence of the frequent passage of macroscopic blood and bloody mucus in the stools. The occurrence of bleeding and its constancy in carcinoma are so striking that more emphasis than otherwise may be placed on its absence in diverticulitis. Carcinoma is essentially a mucosal involvement, whereas the most constant process in these cases is extramucosal—a true peridiverticulitis. Of the 17 cases reviewed, 1 only gave a history of macroscopic blood, and in this instance there was a partial intussusception of the sigmoid into the rectum, which alone would satisfactorily account for the variation.

The preceding discussion refers to the group of 17 cases of nonmalignant lesion of the sigmoid. The remaining 5 cases of diverticula of the sigmoid showed carcinomatous degeneration, and gave a history of abdominal pain for nine months, one year, four, five, and twelve years, respectively. Three of the group gave a long history, suggesting the possibility of a preceding inflammatory lesion. The frequent passage of macroscopic blood occurred in all but 1 of the 5 cases showing malignancy; in this one there was marked chronic obstruction.

In the 2 cases in the colon near the hepatic flexure the clinical histories were in no way definite. One was carcinomatous. The 2 cases in the rectum gave symptoms and findings suggesting carcinoma. One specimen on pathologic examination did not show carcinomatous degeneration. Here again the patient having a simple peridiverticulitis presented a mass which was very hard and adherent, and gave no history of the passage of macroscopic blood, while the duration of the symptoms was three years. The patient having a carcinomatous lesion gave a seven months' total length of history, with the passage of blood during this period.

The one case of diverticulitis of the anal ring was clinically in all respects similar to anal fistula.

Five of the 27 patients died, 1 of these of cerebral hemorrhage forty days after operation, and another of nephritis on the twenty-first day (autopsy). The direct mortality was, therefore, 3, or approximately 11 per cent.

COMPARISON WITH CASES REPORTED

A review of the literature has been made for the purpose of comparing the clinical data obtained with our own observations. A satisfactory description of diverticula demonstrated at operation or in the surgical or postmortem specimen in addition to a clinical history was essential in order to make the review of definite value. These requirements were not met by most of the reports, and consequently it was possible to obtain only 36 cases for tabulation, and in most of these the clinical data were not complete. The age of the patient, the character of the pain, the nutrition, and the demonstration of a mass correspond very closely to the findings in our own series. Twenty-four of the 36 patients were between forty-five and sixty years of age. Six instances of acute perforation with general peritonitis occurred. In 27 of the remaining 30 a mass in the left iliac fossa was demonstrated clinically. In only 3 of the 36 was a history of macroscopic blood in the stools noted. In 3 it was definitely stated that no blood had been seen, and it is likely that so important a point would generally be recorded if positive.

Similarly, for purposes of comparison, 100 consecutive histories of carcinoma of the sigmoid from our own files were reviewed. Of this number, 74 gave the frequent passage of blood and mucus in the stools as a most prominent and constant symptom; in 17 no definite statement was made, while in 9 with severe obstruction it was stated positively that blood and mucus had not been seen.

SUMMARY

In the light of these findings, then, it would seem that a probable clinical diagnosis of diverticulitis of the sigmoid may be made in certain cases. Given a patient with a tumor of the sigmoid, the points in the evidence which would favor a diagnosis of the chronic proliferative type of diverticulitis are as follows: (1) The absence of those shadows of malignancy in the general picture; (2) a tendency to obesity and the maintenance of good nutrition; (3) a *long* history of attacks of low abdominal pain, localizing in the left lower quadrant; (4) a history of the formation of a mass and its subsequent disappearance; (5) a failure to obtain a more or less continuous history of the frequent passage of macroscopic blood in the stools; (6) the demonstration of vesical fistulas which, on cystoscopic examination, appear to be inflammatory, and (7) the failure to demonstrate malignancy positively by sigmoidoscopic examination.

In carcinoma of the lower bowel there is usually an early loss of flesh. Pain is not a prominent feature until obstruction advances, and the mass is often found before pain has been complained of at all. Tenderness to pressure is a late finding. The relative frequency must also be kept in mind. In our experience carcinoma of the sigmoid has been only 7 times as frequent as diverticulitis.

The other inflammatory forms of perisigmoiditis cannot be positively differentiated. A diagnosis of appendicitis in cases of transposition of the viscera should not be difficult. If non-rotation of the colon exists, a radiographic or fluoroscopic examination after a bismuth meal would be necessary. It must not be forgotten that a pelvic tumor may be a sigmoidal tumor, and the possibility of diverticulitis is to be considered. Pelvic inflammatory disease may be closely simulated. In fact, diverticulitis should be carefully considered in the diagnosis of all tumors of the left lower abdominal quadrant and of the pelvis.

REFERENCES

1. Mayo, Wilson and Giffin: "Surg., Gyn. and Obst.," July, 1907. Wilson and Giffin: "Amer. Jour. Med. Sci.," November, 1909. Wilson: "Ann. of Surg.," February, 1911. Giffin: "Ann. of Surg.," April, 1911.
2. Graves: "Boston Med. and Surg. Jour.," March 16, 1911.
3. McGrath: "Surg., Gyn. and Obst.," October, 1912.

INTESTINAL DIVERTICULA: THEIR ETIOLOGY AND PATHOGENESIS

WITH A REVIEW OF 27 CASES*

B. F. MCGRATH

In 1853 Virchow pointed out the frequent occurrence of "isolated, circumscribed, adhesive peritonitis" on the colon, particularly on the hepatic, the splenic, and the sigmoid flexure. The origin of such local inflammatory changes in the intestinal wall, in its serous covering, mesentery, and surroundings, he attributed to constipation, thereby sharply differentiating these processes from catarrhal and dysenteric inflammations. Virchow called attention further to the possible sequelæ—adhesions, contractions—which, for their part, furnished the bases for other groups of symptoms. He was unable to describe the clinical picture of these affections, but believed that many of the cases were misinterpreted as inflammations of the gall-bladder and the like.

Little attention was paid to those observations of Virchow, and for many years these pathologic processes were overlooked.

As Bittorf (1909) indicates in his contribution on "pericolitis," interest in the subject was awakened by Windscheid (1889), who described three cases of acute exudative inflammation involving the entire ascending colon. In the following years several cases, including acute, subacute, and chronic processes, with various complications, and involving, for the most part, the flexures of the colon, were reported by numerous writers.

Among the causes attributed to the cases cited by Bittorf are extension of infection from surrounding structures; protracted, severe catarrhal and dysenteric affections, intestinal ulcers (tuberculous, syphilitic, typhoid, carcinomatous, etc.), constipation and diverticula, the last especially in those cases in which the sigmoid was involved.

---

* Read before the Norfolk District Medical Society, Boston, January 30, 1912. Reprint from "Surgery, Gynecology, and Obstetrics," October, 1912, pp. 429–444.

Graser (1899) was the first to demonstrate the association of acquired diverticula with these pathologic processes of the intestine, but it remained for more recent investigators to discover the comparative frequency of the pouches and their etiologic rôle in what might be termed *extramucosal* intestinal inflammations.

From a comparison of the pathology so excellently described by Virchow and other older writers with the pathologic processes rather frequently noted in late years in connection with intestinal diverticula, it seems fair to assume that in some of those early cases diverticula were present, but overlooked.

Diverticula have been observed in every division of the digestive tube, from the beginning of the esophagus to the end of the rectum, including the vermiform appendix.

This paper is limited to a discussion of intestinal diverticula, particularly those occurring in the large bowel.

That intestinal diverticula may occur in any decad of life, but are comparatively frequent in the middle and, especially, the late period; that they are most commonly present in the large intestine, usually in the descending portion; that in at least 60 per cent. of cases they are a source of infection with results sufficient to produce symptoms; that they are the bases of gravest pathologic processes and sequelæ; that the opinions concerning their etiology and pathogenesis have been lacking in uniformity, and, because of this, a clear conception of the symptomatology is, in general, wanting; finally, that, owing to the indefinite clinical aspect, early stages of inflammation have been overlooked or misinterpreted, its advanced stages diagnosticated malignant and, in consequence, inadequate, sometimes seriously deficient, treatment employed, are facts supported by the literature, by experimental, anatomic, clinical, and pathologic investigations.

Despite these facts, owing to the paucity of practical contributions on the subject in medical journals which are far-reaching, and a complete absence from many text-books of even recent publication, the frequency of these defects of the intestinal wall, their pathogenesis, their clinical and surgical significance, have not been duly appreciated by the medical profession in general.

A brief recital of some observations which have been made in the history of this subject should serve to emphasize the importance of these diverticula and act as a stimulus to keen interest in the question.

At autopsy, Hansemann demonstrated 400 diverticula (small and large intestine) in one case (male, aged eighty-five years, death from pneumonia); Cruveilhier, 200, Hodenpyl, 79, and Kivlin, over 40, respectively, in a single colon. Treves cites a case in which the entire sigmoid was studded with pouches. The writer has counted 44 from the splenic flexure to the upper rectum.

Graser found diverticula 10 times in 28 cases (35.7 per cent.); Sudsuki, 15 times in 40 (37.5 per cent.); the writer, 7 times in 21 (33.3 per cent.).

In the small intestine the diverticula have been observed almost invariably along the mesenteric border (Fig. 13), were usually empty, and but one case has been noted in which infection of them gave rise to symptoms (Gordinier and Sampson).

In the large intestine the diverticula have been demonstrated more frequently aside from the mesentery, commonly in relation to the appendices epiploicæ, most constantly in the sigmoid, and were the source of pathologic processes varying in degree from mild to the gravest.

The *size* of the diverticula varied from microscopic to that of a hen's egg—average size about that of a large pea.

The *shape* was usually round or ovoid. The smaller, especially, were frequently flattened and their long axis transverse, parallel with the bundles of the circular layer of the muscularis. The greater number were sessile; the pedunculated were rather globular in form.

In *structure* the majority of the advanced diverticula consisted of mucosa, submucosa, and serosa. Some were composed of all the mural layers.

Their *openings* into the intestinal lumen varied in diameter from nearly that of the diverticular cavity to a diameter much narrower, thereby, in the latter case, a stenosis of the exit resulting.

The *content.* Excepting those occurring in the small intestine, the diverticula contained fecal matter, varying in consistence from that of the intestinal lumen to firm concretions. In some cases foreign bodies were found. Concretions have become encapsulated within diverticula and, the pedicles sloughing, thus giving rise to free foreign bodies in the abdominal cavity.

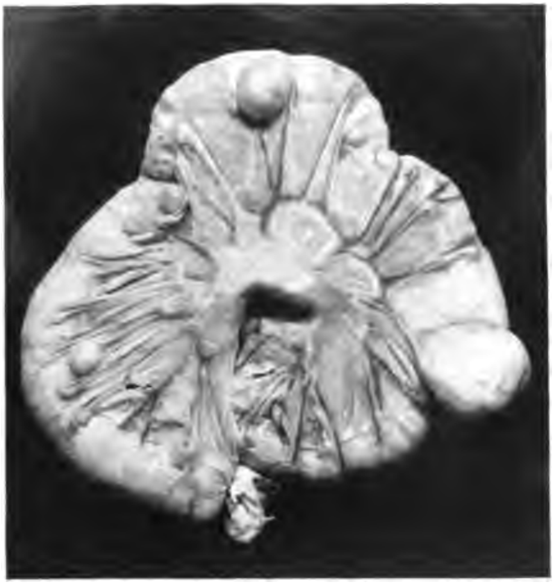


Fig. 13.—Case No. 44310.—Autopsy series. No symptoms. A section of the jejunum showing multiple diverticula along the attachment of the mesentery and their relation to the blood-vessels.

Telling cites 105 cases presenting diverticula, 60 per cent. of which were attended by symptoms. In 80 of Telling's collection the age and sex are given. Of this number, 54 are males and 26 females.

Thirty-three cases presented no symptoms which attracted attention to the diverticula, the latter having been incidentally discovered.

PATIENTS WITHOUT SYMPTOMS

Decads	No. of Cases
1st to 4th, included	0
5th	3
6th	2
7th	13
8th	13
9th	2
Total	33

Forty-seven were attended by symptoms due to the diverticula.

PATIENTS WITH SYMPTOMS

Decads	No. of Cases
1st to 2d, included	0
3d	1
4th	4
5th	9
6th	14
7th	15
8th	4
9th	0
Total	47

Youngest case in Telling's collection, twenty-two years (Fielder). Youngest case reported, seven years, nine months (operative diagnosis) (Astley P. C. Ashhurst).

Observed pathologic processes, which resulted from infection through intestinal diverticula:

1. General peritonitis as a result of a thinning of the diverticular walls. In some cases the sac-walls were so thin that fecal matter could be seen through them.

2. Acute or gangrenous inflammation of sigmoid diverticula with symptoms so closely simulating appendicitis as to suggest a transposition of the viscera. Perforation followed by localized abscess or general peritonitis has resulted from this process.

3. Chronic extramucosal inflammation, resulting frequently in large masses, movable or fixed, and sometimes producing stenosis of the bowel. This chronic process was the most constant finding and often gave rise to tumors simulating carcinoma. It

was usually accompanied by inflammation of the diverticular mucosa, but this was frequently not advanced, and in a few cases undiscernible.

4. Adhesions to neighboring structures, notably the bladder, small intestines, pelvic walls, uterine adnexa, and other parts of the large bowel itself. In a few cases acute or chronic obstruction has been produced in the small intestine.

5. Perforation resulting in general peritonitis, local abscess formation, submucous fistulas, and fistulous communications with other structures. Sudden perforation with resultant general peritonitis has followed straining at stool. Abscesses have formed in the intestinal wall, outside the wall, and surrounded by coils of small intestine, in the mesentery, and extending to the liver and left kidney. Abscess formations have simulated carcinoma. Fistulous tracts have resulted between the sigmoid and the small intestine, the abdominal wall, and, most frequently, the bladder. Sudden perforation into the bladder has occurred on lifting a heavy weight. In some cases the fistulous communication was direct between a diverticulum and a viscus, but in others it occurred by way of an interposed abscess cavity.

6. Chronic mesenteritis resulting in thickening, kinks, and, probably, volvulus.

7. The lodgment of foreign bodies has produced diverticulitis, perforation, and local abscess formation.

8. Metastatic suppuration was noted once in the liver.

9. Carcinoma has occurred on inflammatory processes resulting from infection through diverticula.

A Few of the Clinical and Surgical Facts

Cases have been diagnosed malignant clinically, surgically, and at autopsy, and later pathologic examinations have proved the process to be simple inflammation.

A case is cited in which a gradually enlarging tumor was diagnosed malignant at exploration, a bad prognosis given, and within a few months the tumor had disappeared and the patient regained perfect health.

Palliative colostomies have been made in the presence of large masses diagnosed malignant, but the patients lived on, and in some instances were later "cured of cancer" by a healer or a Christian Scientist.

In the literature is reported a death from peritonitis following an exploratory laparotomy, at which a diagnosis of inoperable tumor had been made. Autopsy revealed rupture of a suppurative focus in an inflammatory mass, which was due to acquired diverticula.

In the light of the topographic relations of the large intestine, its physiologic function, the occurrence of diverticula, and the resultant pathologic processes which have been cited, one may see the many possible sequelæ arising from infection through these pouches.

In contemplating even this inadequate review of the pathology of others' cases, together with a few of the clinical and surgical experiences of the past, do we not find food for reflection and a reason for interest in the subject of intestinal diverticula?

These diverticula have been classified as—(1) congenital, and (2) acquired. The congenital class has its origin in defective embryologic development, and Meckel's diverticulum is a type. The so-termed acquired class is generally considered as independent of developmental deficiency, but it has been suggested that some of these also are, in a certain sense, congenital.

Two types of this class have been recognized: one in which all layers of the intestinal wall are involved, the other in which only some of the layers take part. These definitions refer to the developed diverticula, not to the initial stages in their formation.

The structure of the incomplete type, termed "false" diverticula, usually consists of mucosa, submucosa, and serosa. This is by far the more common form of acquired diverticula and has been described as a "hernia mucosæ." The latter term well expresses the formative process, which consists of a protrusion of the mucosa through a weak point in the muscularis.

The diverticula in this series of cases are of the acquired class and limited to the large bowel.

Statistical data of cases operated on by W. J. and C. H. Mayo at St. Mary's Hospital from May 1, 1902, to January 1, 1912:

Number of cases	27

(Twenty-five specimens were obtained from operation, one from autopsy. One case was drained; surgical diagnosis, diverticulitis.)

Sex—

Males	21
Females	6

Age—

Youngest	40 years
Oldest	73 years
Average age	54 years

OCCURRENCE IN DECADS

Decads	No. of Cases
1st to 4th, included	0
5th	9
6th	12
7th	5
8th	1

OPERATIONS

Resection	21
Partial resection	4
Ileocolostomy	1
Drainage	1

LOCATION OF INITIAL DISEASE

Sigmoid	20
Sigmoid and rectum	1
Rectum (at anal ring)	3
Hepatic flexure	2
Descending colon	1

CLASSIFICATION

	Frequency in Cases
1. Peridiverticulitis	26
Peridiverticulitis, advanced	22
2. Diverticulitis	24
Diverticulitis, advanced	5
Diverticulitis, slight to moderate degree	19
Diverticulitis, undiscernible	2
3. Ulceration (usually slight)	11
4. Perforation	6
5. Abscess formation (wall of sigmoid at inner side of sigmoid mesentery, above hepatic flexure, and in liver)	4
6. Adhesions (posterior wall of bladder, ileum, pelvic wall, uterine adnexa)	5
7. Fistulous communications (abdominal wall, bladder)	2
8. Stenosis (Marked, 1; moderate, 7; slight, 5).	13
9. Carcinoma (25.9 per cent.)	7

Tuberculous peritonitis was associated with one case.

The diverticula were nearly all of the incomplete type,—"false" diverticula,—multiple, and most commonly associated with the appendices epiploicæ. The majority of the pouches contained fecal matter, usually inspissated, and in several fecoliths were present. The resected masses varied in size from a few centimeters to more than 30 cm., and contained much fat with dense areas. The mucosa encircling many of the diverticular openings was somewhat edematous.

MORTALITY, 18.5 PER CENT.

CASE 4.—W. J. M., female, aged fifty-two years. *Diagnosis,* peridiverticulitis, tuberculous nodules on the peritoneum. *Cause of death,* general peritonitis eighteen days after operation.

CASE 5.—W. S., male, aged fifty-two years. *Diagnosis,* diverticulitis, peridiverticulitis, ulceration of the mucosa. *Cause of death,* general peritonitis thirteen days after operation.

CASE 10.—M. D., male, aged forty-eight years. *Diagnosis,* carcinoma on peridiverticulitis in rectum. *Cause of death,* cerebral hemorrhage forty days after operation.

CASE 14.—C. M. J., female, aged fifty-three years. *Diagnosis,* peridiverticulitis, obstruction, abscess in sigmoid. *Cause of death,* pelvic peritonitis, parenchymatous degeneration of organs, nephritis, two days after operation.

CASE 19.—W. R. B., male, aged fifty-eight years. *Diagnosis,* diverticulitis, peridiverticulitis. *Cause of death,* toxemia, parenchymatous degeneration of organs, nephritis, twenty-one days after operation.

The natural questions which present themselves before one investigating this subject are: What factors are concerned in the origin of these diverticula? What are the causative factors and steps in their pathogenesis? What is the most constant pathologic process resulting from infection through them?

In an endeavor to answer these questions the writer undertook experimental, anatomic, and histologic examinations of the specimens removed at autopsy, in conjunction with the study of the pathologic specimens.

Various methods of experimental investigation were employed, but the results from the use of a gelatin preparation were the most satisfactory.

After the fresh specimen had been filled with the liquefied gelatin it was placed in a 10 per cent. solution of formalin and allowed to harden.

The experimental series consists of 21 large intestines and portions of a few small intestines.

OCCURRENCE IN DECADS

DECADS	NO. OF CASES
1st to 3d, included	0
4th	1
5th	1
6th	0
7th	1
8th	2

(Ages of two cases were misplaced)

On examination of the accumulated fixed specimens, 7 (33.3 per cent.) presented the following points:

External Aspect (Fig. 14).—On the surface of the large bowel were prominences, varying from a minute size to that of a small cherry. The shape was generally round or ovoid. Some of the smaller were oblong with the long axis transverse. In a few cases the surface between the longitudinal muscular bands presented a "ribbed" appearance, the elevations running parallel with the fibers of the circular muscular layer and suggesting a bulging of the mucosa between the bundles (Fig. 15).

The greater number of the circumscribed elevations, and generally the largest, were observed in close relation to the bases of the appendices epiploicæ. In but one of these specimens were the epiploic appendages noted as especially large. In a few instances the prominences were at the mesenteric border or between the layers of mesentery, and some were situated elsewhere on the sacculi. The latter were usually small and commonly located on the summit or close to the constrictions between the sacculations.

Dissection revealed the prominences corresponding in general to those points where the vessels disappear into the muscular layer of the intestinal wall.

The entrances of the larger vessels were commonly noted near

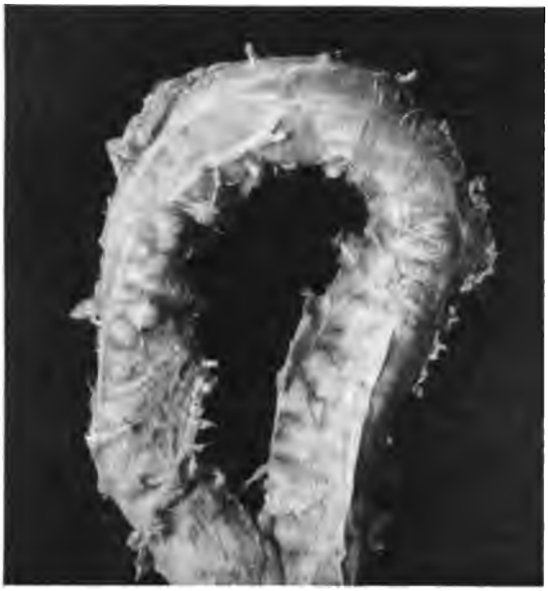


Fig. 14.—Case No. 44310. Autopsy series. No symptoms. Same as case Fig. 13. Sigmoid and upper rectum, showing diverticula along the attachment of the mesentery and also in relation to the appendices epiploicæ.

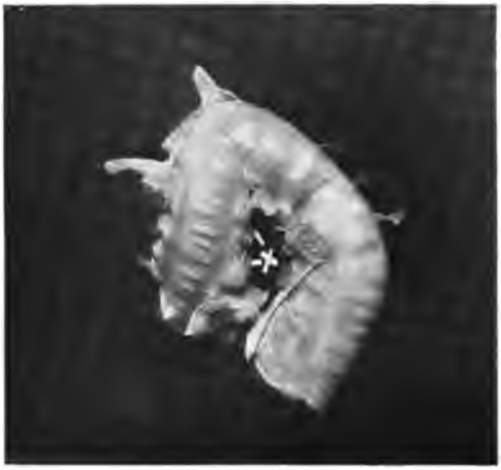


Fig. 15.—Case No. 43978. Autopsy series. No symptoms. Sigmoid, showing diverticula, "X," in relation to the appendices epiploicæ, and the "ribbed" appearance on the surface between the longitudinal bands.

the edges of the longitudinal bands, sometimes inside the edges, between widely separated bundles of the muscular fibers. The entrances of the smaller branches were variously situated on the haustra.

Each set of vessels was covered with a band of fat, which, in the case of the larger branches, was continuous with that of the mesentery and terminated as an epiploic appendix in close relation to the vascular entrance.

To be noted, therefore, were the frequent occurrence of these prominences at the points of entrance of the large vessels and the relation of the latter to the bases of the appendices epiploicæ (Fig. 16).

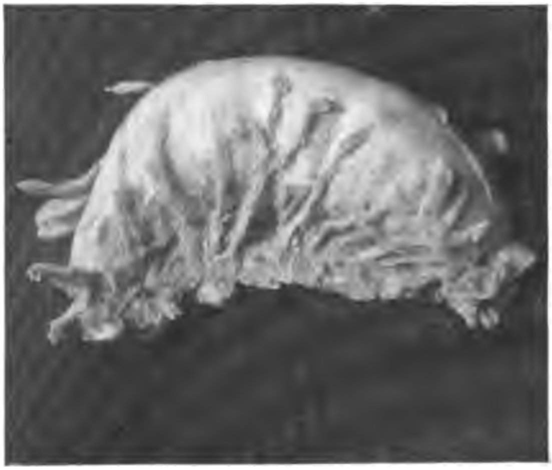


Fig. 16.—Case No. 44009. Autopsy series. Sigmoid. The appendices epiploicæ have been removed in order to show the vascular entrances into the intestinal wall.

Internal Aspect (Figs. 17 and 18.)—On the mucosal surface of the same specimens defects were noted, which appeared in some places as round or oval openings, in others as short, transversely placed clefts. From these points plugs containing gelatin were expressed, and then thin-walled pouches demonstrated. These openings on the inner surface corresponded in location to the elevations on the outer surface (Figs. 19, 20, 21).

Histologic examinations confirmed the experimental and anatomic observations as to the common association of these processes with the course of vessels through the intestinal wall.

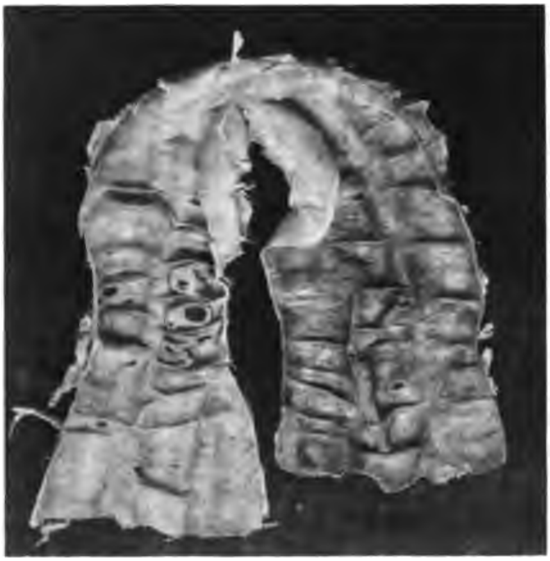


Fig. 17.—Case No. 44310. Autopsy series. Internal aspect of specimen in Fig. 14, showing the variations in size and shape of the diverticular openings.

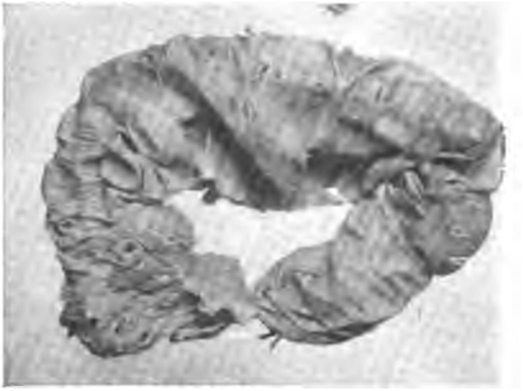


Fig. 18.—Case No. 43987. Autopsy series. Sigmoid of another case; conditions similar to those in Fig. 17.

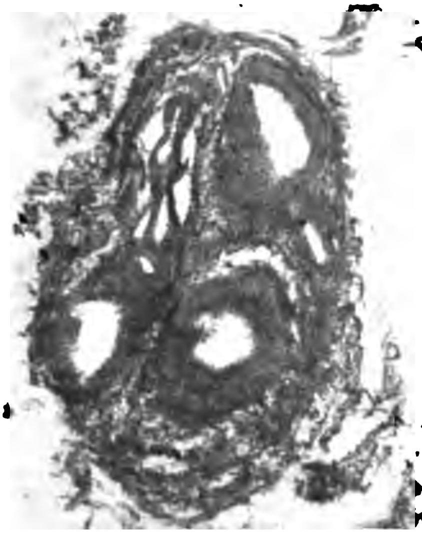


Fig. 19.—Autopsy series. Low-power photomicrograph, showing the set of vessels frequently found passing in association with diverticula through the wall of the large bowel.

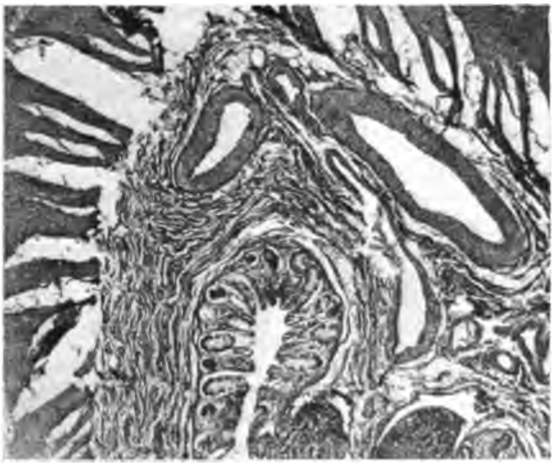


Fig. 20.—Case No. 43987. Autopsy series. Low-power photomicrograph, showing a small diverticulum, vessels, and separated muscular bundles of the circular layer.

Examination of the muscular coat of the large bowel showed that the longitudinal layer, excepting in the three bands, was usually very scant or entirely wanting, and that frequently the circular layer was thin, its bundles separated, and, consequently, its structure deficient.

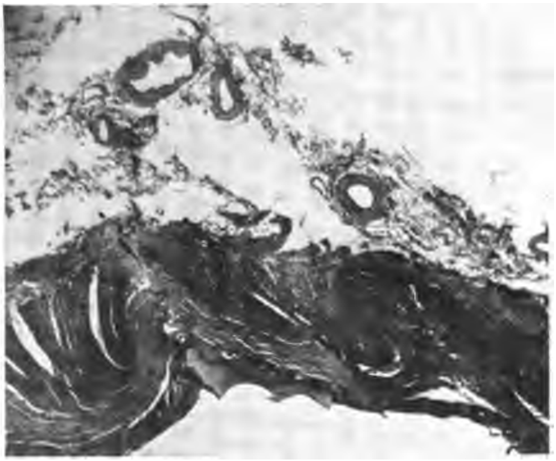


Fig. 21.—Case No. 43858. Autopsy series. Low-power photomicrograph, showing the course of vessels through the muscular layer of the intestinal wall and indicating points of weakened resistance.

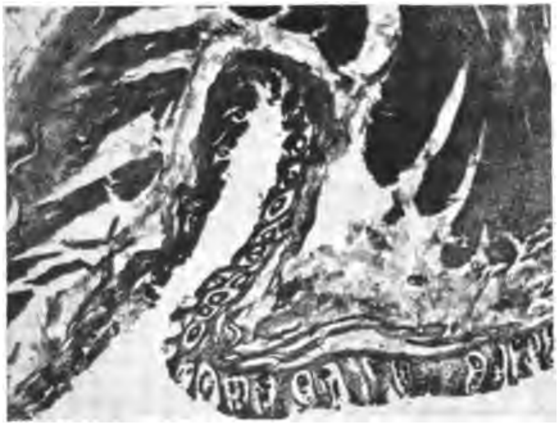


Fig. 22.—Case No. 43978. Autopsy series. Low-power photomicrograph, showing a small diverticulum separating muscular bundles of the circular layer.

In some instances microscopic examinations revealed beginning projections of the mucosa and submucosa between widely separated bundles of the circular muscle, without the presence of vessels directing their course (Figs. 22 and 23).

Besides the processes which have been described, there were occasionally observed a marked bulging and thinning of a sacculus, especially in the lower part of the sigmoid, where the sacculations of the bowel are smaller.

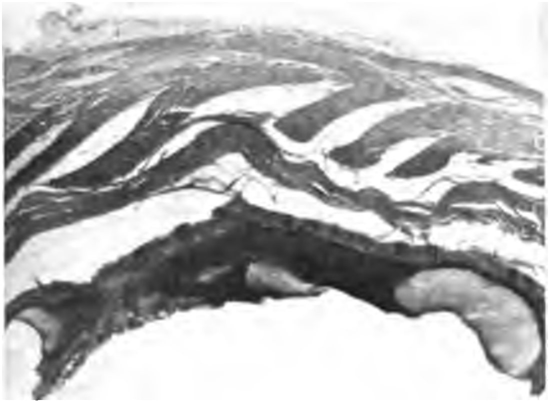


Fig. 23.—Case No. 43978. Autopsy series. Low-power microphotograph, showing the muscular bundles widely separated and a beginning bulging of the mucosal and submucosal layers between them.

ETIOLOGY

Views on the causation of acquired diverticula of the intestine have been advanced by numerous authors, notably Graser, Klebs, Hansemann, W. J. Mayo, Wilson, Sudsuki, Beer, Telling, Edel, Heschl, Hanau, Good, Chlumsky, Schreiber, and others.

The causal factors cited are: (1) Obesity; (2) cachexia and absence of fat; (3) a previous state of obesity and subsequent wasting; (4) normal structure of the large intestine; (5) physiologic rôle of the sigmoid flexure; (6) intraintestinal pressure; (7) relation of diverticula to points of entry of vessels through the intestinal wall; (8) variations in the size of vessels, resulting from varying blood-pressure—in chronic heart disease, etc.; (9) congenital predisposition with regard to the amount and laxity of the connective tissue surrounding the vessels; (10) muscular deficiency of the intestinal wall.

From an analysis of the cases and investigations cited in the literature, together with the cases and the observations in this series, the writer has made the following deductions:

No single factor explains the origin of acquired diverticula in the large intestine, but the process results from a summation of several factors.

In the formation of the more common type—"false" diverticula, "hernia mucosæ"— are to be seen the same factors which contribute to the production of typical hernia elsewhere in the body, namely, insufficient resistance of the wall, increased pressure from within, the passage of a structure through the wall, forming a "locus minoris resistentiæ," along which the protrusion makes its course.

That diminished tone of the intestinal musculature may result from general degenerative changes, debilitating diseases, and senility is self-evident. It is very probable that local conditions within the bowel also contribute to the mural weakness. Several cases present a history of chronic constipation.

It is also conceivable that congenital muscular insufficiency may be present here as well as elsewhere in the body. The young patients, and those in early middle life, who give no previous history of general debilitating or local intestinal disease, suggest the plausibility of that assumption.

That the factor of pressure from within is present in the large bowel is evident from the function of this division of the digestive tube, and, as is well recognized, this force is frequently accentuated by abnormal accumulations of gas and stasis of the intestinal contents, especially in the sigmoid flexure.

Normally, the tissue surrounding the vessels in their course through the muscular wall is less resistant than the muscular layer itself, and it is natural to suppose that its resisting power will also be weakened by the same conditions which affect the musculature. Furthermore, it is conceivable that circulatory disturbances from whatever cause, which produce chronic congestion of these vessels, with intervals of lowered blood-pressure, would decrease still more the resistance at these points and thereby facilitate the protrusion of the mucosa.

The other, more rare type of acquired diverticula, in which all the mural layers are involved, is probably the effect of a localized weakening of a sacculation, together with traction by adhesions from without, or by exaggerated pressure upon this point from within. It is to be noted that congenital diverticula may also occur in the large bowel. The process observed, in which the mucosa tended to bulge outward between separated muscular bundles and appeared independent of the course of vessels, is very likely due to exceptionally insufficient structure of the muscular layer. This condition may account for some of the infections in which typical diverticula are not demonstrable.

All authors have noted the frequent presence of diverticula in relation to the appendices epiploicæ. Telling says: "Bland-Sutton has stated and illustrated by diagrams that this fat is directly continuous with the subserous fat." And that author adds: "If there is the slightest tendency to the formation of diverticula, it will readily be seen that the soft fatty tissue of the appendix forms a point of lowered resistance."

From the writer's observations on a limited series, it would seem that this relationship between diverticula and appendices epiploicæ is due to the fact that these fatty masses are situated either directly on or close to the points where the larger vessels enter the intestinal wall, since they are the terminations of fat-bands, extending from the mesentery and covering these vessels.

Pathogenesis.—In the observations on the etiology it has been seen that the most common type of the diverticula consists of a protrusion of the mucosa and submucosa through the muscular layer of the bowel. The form varies from straight pouches with large sufficient openings, to those of flask shape, constricted at the neck by the perforated muscular layer, with the bulged-out body beneath the serosa.

As was previously noted, they are practically always filled with fecal matter, varying in consistence from that of the normal to hard concretions. Although the mucosa of some diverticula appears intact, yet, as a result of the continued mechanic pressure and toxic irritants, the lining epithelium is frequently injured, varying in degree from atrophy to ulceration.

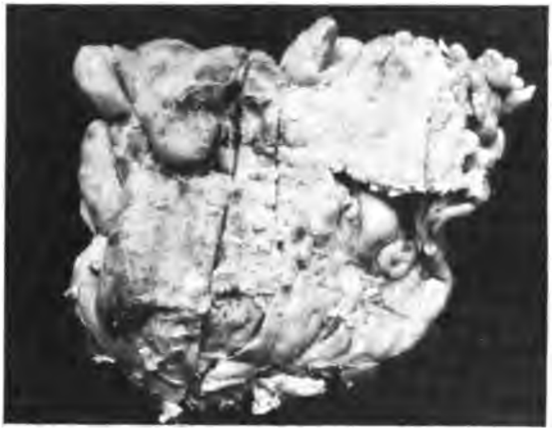


Fig. 24.—Case No. 40506. Pathologic series. External appearance of a resected mass. Diagnosis: Peridiverticulitis.

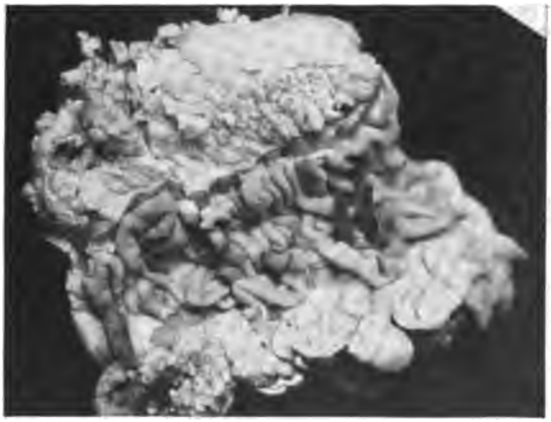


Fig. 25.—Case No. 40506. Pathologic series. Same specimen as in Fig. 24. Mucosal aspect, showing probes inserted in diverticula.

Associated with these processes there is usually an extramucosal round-cell infiltration. As the diverticulum enlarges there occurs

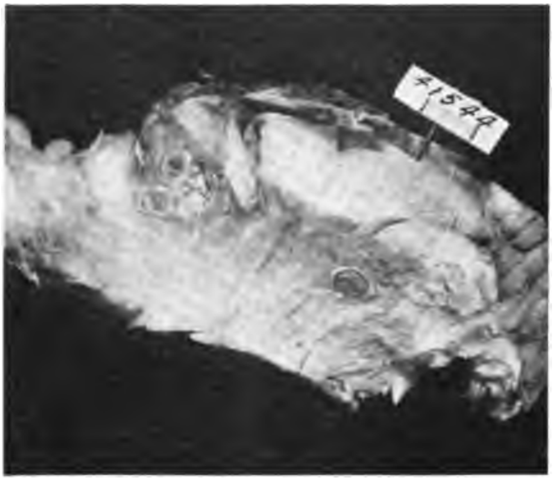


Fig. 26.—Case No. 41544. Pathologic series. Transverse section of a specimen, showing multiple diverticula filled with fecal matter, dense areas of fat. Diagnosis: Peridiverticulitis and diverticulitis.

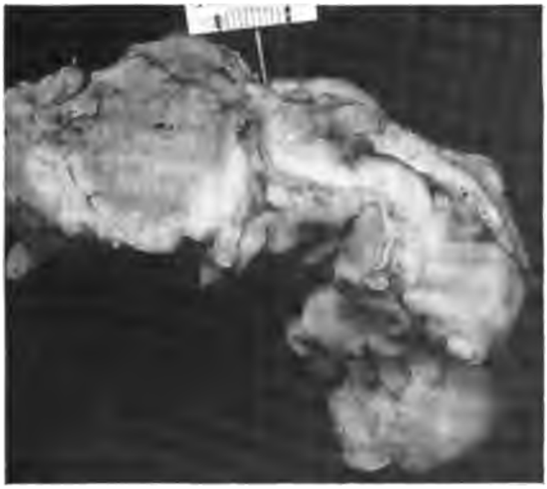


Fig. 27.—Case No. 40506. Pathologic series. Longitudinal section of a diverticulum, showing also the dense areas and fat. Same specimen as in Fig. 25. Diagnosis: Peridiverticulitis.

a thinning of the walls of the sac, which may reach such an extreme degree that only a film of peritoneum separates the diverticular lumen with its fecal content from the peritoneal cavity. This condition has led to general peritonitis, due to osmosis of bacteria or their toxins.

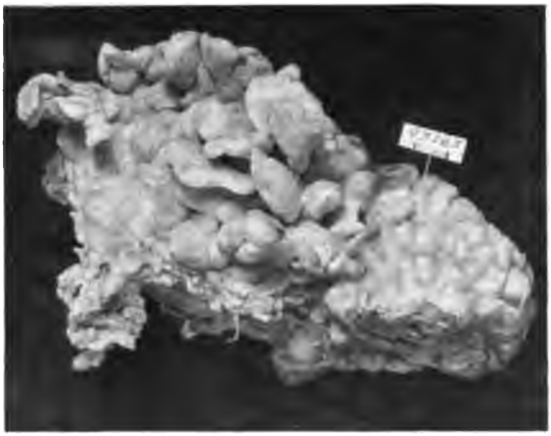


Fig. 28.—Case No. 43163. Pathologic series. External aspect of a resected mass. Diagnosis: Carcinoma; peridiverticulitis.

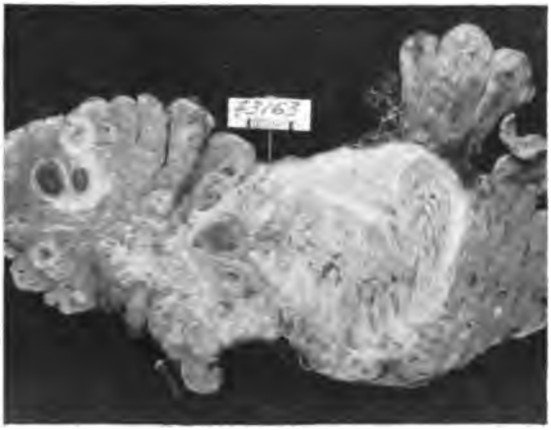


Fig. 29.—Case No. 43163. Pathologic series. Transverse section of specimen in Fig. 28, showing multiple diverticula containing fecal matter, dense areas, and fat. Diagnosis: Carcinoma; peridiverticulitis.

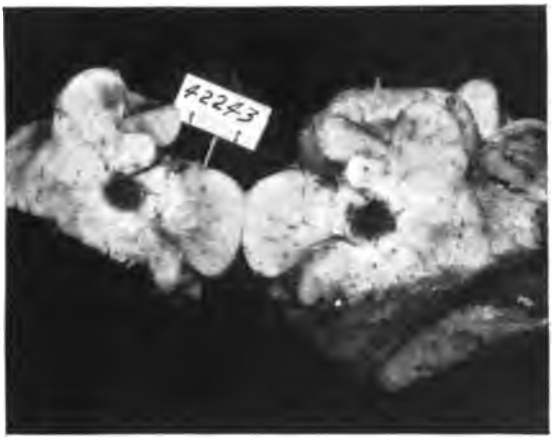


Fig. 30.—Case No. 42243. Pathologic series. Transverse section of an enlarged epiploic appendix, showing a diverticular lumen filled with fecal matter. Diagnosis: Carcinoma; peridiverticulitis.

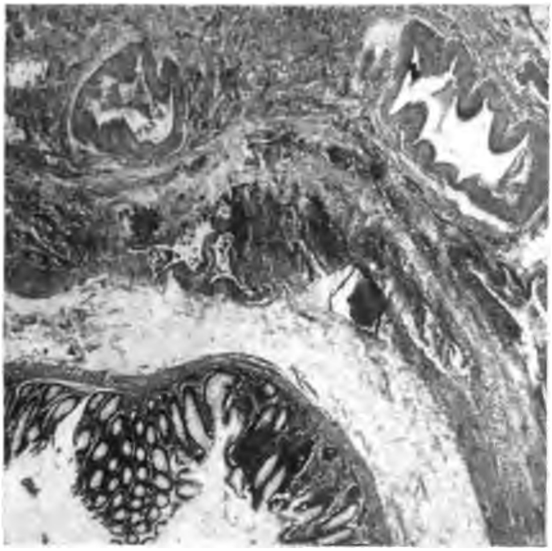


Fig. 31.—Case No. 40506. Pathologic series. Low-power photomicrograph. A section from the specimen in Fig. 27, showing pronounced peridiverticulitis.

The result of incarcerated concretions varies from slight abrasion of the mucosa to perforation through the wall of the sac.

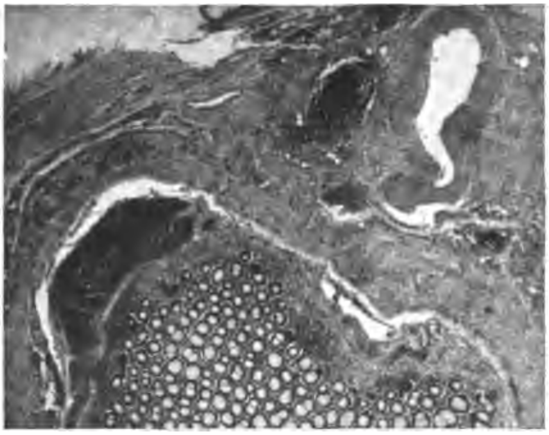


Fig. 32.—Case No. 43163. Pathologic series. Low-power photomicrograph. A section from specimen in Fig. 29, showing only peridiverticulitis. Diagnosis: Carcinoma; peridiverticulitis. (See Fig. 33.)

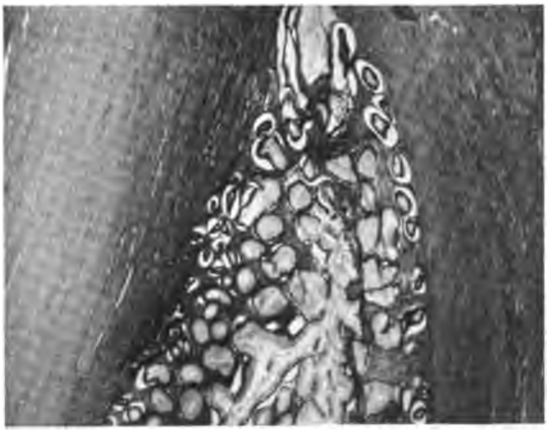


Fig. 33.—Case No. 43163. Pathologic series. Low-power photomicrograph. Section from same case as in Fig. 32, showing carcinoma and peridiverticulitis.

The sequelæ of such perforation may be—(*a*) General peritonitis; (*b*) local abscess formation; (*c*) submucous fistulas; (*d*) fistulous communications with other viscera and the abdominal wall. Perforation may occur suddenly, the result of straining.

Owing to the extreme constriction at the neck and a great accumulation of fecal material, some of these "herniæ mucosæ" undergo strangulation, with resultant gangrenous inflammation. From this process there result abscesses in the intestinal wall, which may rupture into the peritoneal cavity, the lumen of the affected bowel, or any of the neighboring structures.

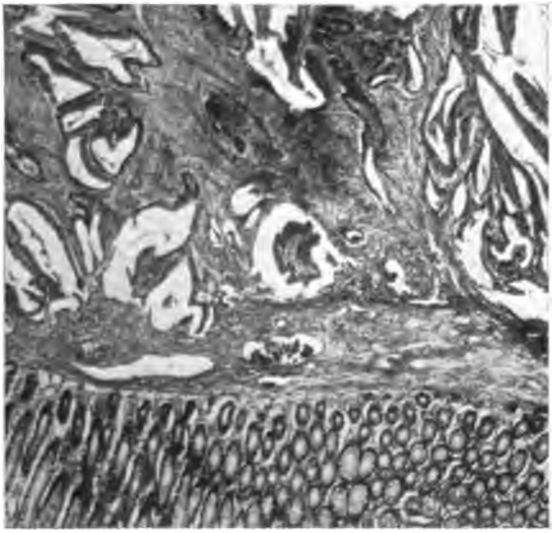


Fig. 34.—Case No. 42243. Pathologic series. Low-power photomicrograph, showing carcinoma. Diagnosis: Carcinoma; peridiverticulitis. (Same case as Fig. 30.)

The most constant pathologic process, and an essential consideration in dealing with infections through these diverticula, is the chronic proliferative extramucosal inflammation (Fig. 31).

In 1907 Wilson emphasized the essential rôle of this process and designated it "*peridiverticulitis.*" Telling (1908), in his excellent contribution to the subject of acquired diverticulitis of the intestine, says: "*Of all the secondary results, this proliferative inflammation is the most important, the most frequent, and probably* *the most overlooked.*" The process is a chronic inflammatory reaction due to leakage of toxins or bacteria through the mucosal layer of the diverticula. This gives rise to the formation of

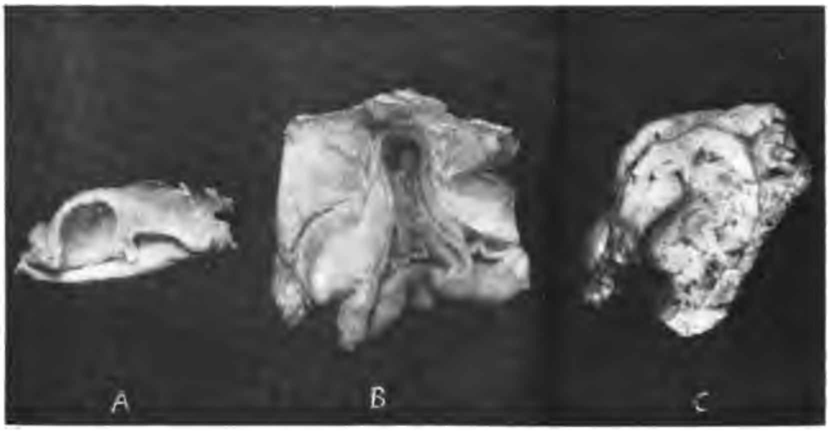


Fig. 35.—Special series—A (43987): A diverticulum from specimen in autopsy series (*no symptoms*). B (40506): A diverticulum from specimen in pathologic series (*peridiverticulitis*). C (43163): A diverticulum from specimen in pathologic series (*carcinoma; peridiverticulitis*).

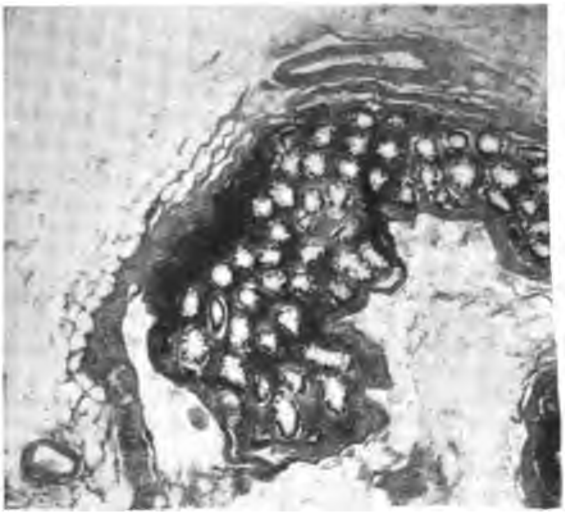


Fig. 36.—Case No. 43987. Low-power photomicrograph. Section from (A) in Fig. 35.

masses, movable or fixed, which may reach great size, produce stenosis of the bowel, and frequently simulate carcinoma. The possible pathologic complications are obvious.

This process was noted in the great majority of cases which have been reported, was present in all the 26 specimens of this series, and advanced in 22.

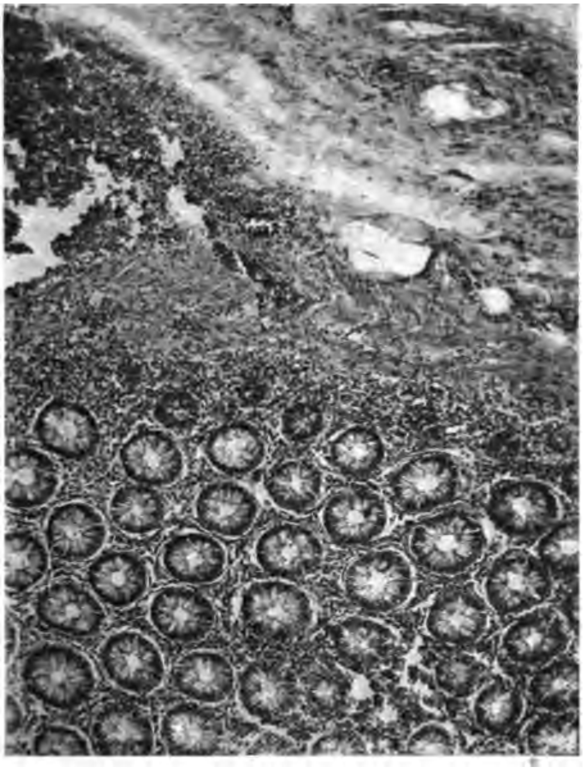


Fig. 37.—Case No. 40506. Low-power photomicrograph. Section from (B) in Fig. 35.

To be emphasized is the fact that this chronic inflammation is commonly the most important initial change following infection through the diverticula, and may be present with little or no discernible inflammation of the mucosa. Thus, in our 26 specimens presenting peridiverticulitis, in only 5 was the mucous membrane of the diverticula extensively involved, in 19 its inflammation varied from mild to a moderate degree, and in 2 it appeared intact.

These facts are important to the clinician, inasmuch as they indicate that symptoms are not to be expected, at least in the early stages of the pathologic process, from the intestinal lumen. Manifestations on the part of the mucosa of the canal generally appear later in the symptom-complex.

It follows from a consideration of the lesions which have been described that adhesions to neighboring structures may readily occur and contribute variously to the clinical picture.

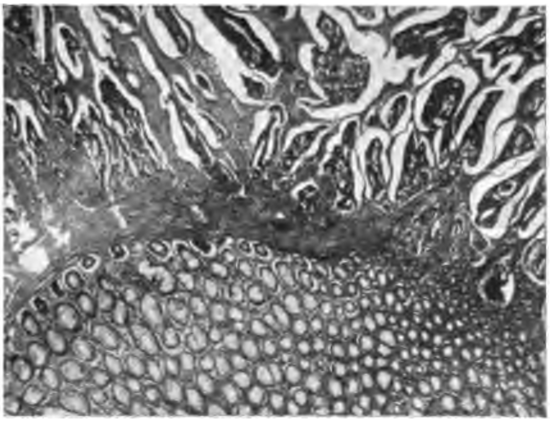


Fig. 38.—Case No. 43163. Low-power photomicrograph. Section from (C) in Fig. 35.

The possibility of a hematogenous infection has been suggested for some of these cases of inflammation in the intestinal wall, but this has not been scientifically supported.

The consensus of opinion is that the infective organisms are in the intestinal canal, and are either exogenous or, more commonly, endogenous, in which case their infecting powers are the result of a perversion of the normal bacterial flora. The conditions associated with the presence of diverticula in the large bowel are most favorable to an increase in the number and the virulence of the intestinal bacteria. The streptococcus has been found in some of the cases resulting in fatal peritonitis.

Of gravest importance is the frequency with which, in recent times, carcinoma has been found implanted on the inflammatory processes of acquired diverticula, particularly in the sigmoid.

As stated above, in the 27 cases of this series, carcinoma was present in 7 (25.9 per cent.). All of these were cases of advanced peridiverticulitis.

In considering this percentage (25.9), however, it is of the strictest importance for us to distinguish between the *occurrence of diverticula in general,* many cases of which are discovered incidentally at autopsy, and cases of diverticula with *pathologic processes* so extensive as to give *pronounced symptoms.*

In our 27 cases the inflammatory changes were advanced, a mass was present in each, and the symptoms were marked. Therefore, *it is in such cases as these alone that the* percentage (25.9) of carcinoma is to be considered.

That irritative conditions such as are present in these infections of intestinal diverticula are contributing causes to carcinoma is a view supported by the observations of several authorities. Among the causes cited are chronic inflammation, cicatrices, bacterial irritation, and trauma. From evidence based on over 1200 personal observations, Coley concludes: "Local trauma of any kind, from chronic irritation to a single local contusion, is not infrequently the direct exciting cause of malignant tumors of all types."

Clinical Diagnosis.—In reviewing the clinical aspect of cases cited in the literature and those of this series it is instructive to note the possible errors in diagnosis and the gradual increase in clinical recognition of diverticular infections by those whom experience with several cases has impressed. Among the diagnoses which have been made are the following: carcinoma of the large bowel, carcinoma on diverticulitis, affections of the gall-bladder, liver, pancreas, and duodenum, appendicitis, pelvic peritonitis, ovarian tumor, etc. As was natural, in the earlier cases with masses involving the sigmoid and upper rectum, occurring, as they usually do, in the so-called cancerous period of life, the diagnosis of malignancy was commonly made. From the knowledge acquired through operation and pathologic reports, the clinical diagnoses have become more conservative and several of the more recent cases of this series were positively diagnosed before operation.

As Telling's report shows, a very great number of these masses have been removed and their true pathology not learned until long afterward, when they were subjected to a detailed pathologic examination.

With the assistance of the clinical pathologist a great majority of the cases may be diagnosed during operation, but some require a further pathologic investigation in detail. Thus, it may be seen that, generally speaking, the final diagnosis rests with the pathologist; therefore, the prognosis should be withheld until such examination has been completed.

Pathologic Examination.—As previously stated, the resected specimen frequently consists of a mass, very fatty, with dense areas (Figs. 24 and 28). On opening the piece of intestinal tube the mucosa is often found intact, excepting that in some cases the rugæ are more pronounced, and pits with edematous margins may be noted. A narrow glass probe with blunt end is very gently inserted wherever these pits present themselves, and frequently they prove to be the openings of diverticula (Fig. 25).

It is misleading to view the external surface of the mass with the idea of seeing the diverticula in the form of projections. Whereas such prominences are characteristic of the cases incidentally discovered at autopsy (Fig. 14), they are rarely seen in the large masses resulting from infection, but instead are usually deep beneath the surface.

The writer has found the method described by Wilson most satisfactory for detecting the diverticula so situated. This procedure consists in making thin slices of the mass, beginning on the external surface, and keeping the blade of the knife parallel with the wall of the bowel.

Examine even the smallest opening that presents itself during the slicing process. The more characteristic of these appear round or oval, encircled by a narrow whitish rim and lined with mucous membrane (Figs. 26 and 29). If an opening represent a severed diverticulum, the inserted glass probe passes easily into the lumen of the bowel, unless, as sometimes happens, the diverticular exit is obstructed as a result of the pathologic processes.

The detailed examination consists in the microscopic study of transverse and longitudinal sections of the diverticula and of all doubtful areas in the mass.

SUMMARY

1. Diverticula of the large bowel may be present at any time of life, but are comparatively frequent in the middle and the late period. They occur in every division of the large intestine, but are most commonly found in the descending portion, especially the sigmoid. They are usually multiple, of the false type, and frequently in close relation with the appendices epiploicæ, but are sometimes found at the mesenteric border, between the layers of the mesentery and elsewhere on the sacculi.

2. According to Telling, in at least 60 per cent. of the cases presenting diverticula there result pathologic conditions which produce symptoms.

3. Infection through these pouches gives rise to pathologic processes and sequelæ which are often most grave. Among the serious results of such infection are peritonitis, with or without perforation, complicated inflammatory conditions, which are sometimes inoperable or attended with hazardous operative risk, simulation of malignancy, and the development of cancer.

4. A fact to be emphasized is that the most constant pathologic finding in the processes resulting from infection through these diverticula is a *chronic extramucosal inflammation,* which in the early stages at least may be present with little or even no discernible injury of the mucosa. This condition has been designated "*peridiverticulitis,*" and is to be differentiated from "diverticulitis," which term is applicable to inflammation of the diverticulum itself. This extramucosal effect of the infection is an essential consideration for the clinician in constructing the symptomatology, and particularly in seeking early diagnostic signs.

5. A study of the pathogenesis in these cases indicates that symptoms on the part of the intestinal lumen are not to be anticipated, at least in the early stages of the affections. Such manifestations may appear in the advanced stages. Naturally, the clinical picture varies with the advance and complexity of the pathologic process, diseases of neighboring structures being frequently simulated.

6. As stated above, carcinoma may develop on these inflammatory processes, and usually occurs in the sigmoid. But it is important to note that the percentage (25.9) in this series is to be applied only to the cases with advanced pathologic changes and not to the occurrence of intestinal diverticula in general.

7. The cases which have been cited from the literature, together with the review of this series, emphasize another instructive fact, namely, that not every tumor of the large bowel occurring in the so-called cancerous period of life is malignant. Thus, of these 27 cases based on diverticular infections, all presented masses of the large intestine, all occurred in the middle or the late period of life, yet 74.1 per cent. of them proved to be only inflammatory. Some of the cases included in this 74.1 per cent. had been positively diagnosed malignant and bad prognoses given by excellent diagnosticians both in this country and abroad, which emphasizes the importance of conservatism in prognosis until the final pathologic report is received.

8. Guided by the comparative frequency of acquired diverticula in the large bowel, especially the sigmoid, the percentage of cases in which infection takes place, the uncertainty as to the frailness of the diverticular walls, the possibility of adhesions to neighboring structures, the presence of abscesses, etc., the surgeon should be scrupulously careful in his manipulation of this division of the intestines. Fatal peritonitis has followed an exploratory laparotomy, autopsy revealing an inflammatory mass due to acquired diverticula.

9. The investigations which have already been made on the etiology and pathogenesis of diverticular affections of the large bowel furnish a foundation for important work on the part of the

clinician and the surgeon. In the present indefinite state of the symptomatology, a knowledge of the comparative frequency of these diverticula, the periods of life in which they most commonly occur and the changes resulting from infection through them, is a preliminary strong point for the diagnosis. In view of the pathologic findings in these conditions the inestimable value of early recognition and adequate treatment is obvious.

LITERATURE

Ashhurst: "Annals of Surgery," 1908, vol. xlvii, p. 300.
Beer: "Amer. Jour. Med. Sci.," July, 1904, vol. cxxviii, pp. 135–145.
Bland-Sutton: "Lancet," London, October 24, 1903, p. 1148.
Bittorf: "Mitteilungen a. d. Grenzgebieten der Medizin und Chirurg.," vol. xx, No. 1, 1909.
Brewer: "Trans. Amer. Surg. Assoc.," 1907, vol. xxv, pp. 258–275.
Chlumsky: "Beit. z. klin. Chir.," 1899, vol. xxv.
Cruveilhier: "Traitè d'anatomie et de pathologie," vol. i, p. 589; vol. ii, p. 492.
Edel: "Virchow's Archiv," 1894, vol. cxxxviii.
Fielder: "Denkschrift der Gesellschaft für Natur- u. Heilkunde," Dresden, 1868.
Gordinier and Sampson: "Jour. Amer. Med. Assoc., 1906, vol. xlvi, pp. 1585–1590.
Graser: "Münch. med. Wochensch.," May 30, 1899; also, "Arch. f. klin. Chir.," 1899, vol. lix.
Hanau: "Virchow's Archiv," 1896, vol. cxlv.
Hansemann: "Virchow's Archiv," vol. cxliv.
Hochenegg: Thirty-first Congress of German Surgeons.
Hodenpyl: "Trans. New York Path. Soc.," March 29, 1900.
Kemp: "Diseases of the Stomach," 1911.
Kendall: "Jour. Med. Research," September, 1911, vol. xxv, No. 1, pp. 117–187.
Klebs: "Path. Anatomie," 1869, p. 271.
Kivlin: "Amer. Jour. Obstetrics," 1906, vol. liv, pp. 843–849.
Mayo, Wilson, and Giffin: "Trans. Amer. Surg. Assoc.," 1907, vol. xxv.
Schreiber: "Deut. Arch. f. klin. Med.," 1902, p. 122.
Sudsuki: "Langenbeck's Archiv," 1900, p. 708.
Telling: "Lancet," London, 1908, vol. i, pp. 843, 928.
Treves: "Intestinal Obstruction," 1899, p. 57.
Virchow: "Virchow's Archiv," vol. v, p. 1853.
Windscheid: "Deut. Arch. f. klin. Med.," 1889, vol. xlv.

DIVERTICULA OF THE GASTRO-INTESTINAL TRACT: THEIR SURGICAL IMPORTANCE*

CHARLES H. MAYO

The various hollow viscera and tubular structures of the body are subject to acquired diverticula. Even the large blood-vessels are prone to this condition in the form of sacculated aneurysm.

Diverticula are classified into two groups—congenital and acquired. For example, a Meckel's diverticulum, or a diverticulum of the urachus connected with the bladder or umbilicus, is a type of the congenital anomaly, while a diverticulum of the esophagus is one of the acquired forms.

True and false diverticula are terms describing the condition with reference to their structure, as compared to the normal walls of the viscus. Those covered with all the coats of the bowel, as represented at its site, are the true diverticula, and those with fewer coats and with the muscularis lacking, at least in part, are the false. True diverticula may later become false by extension beyond their muscular covering, which show in separated bundles over a part of the sac, especially late in life.

The appendix might be termed a normal diverticulum, and the air pouches connected with the larynx in certain species of monkeys might also be so considered. From this latter arose the term "bronchocele," which later was applied to the enlargement of the thyroid gland.

Diverticula of the acquired type are frequently found and described as affecting the gastro-intestinal tract. We note the striking similarity between these sacs or pouches and their process of development. The entire length of the alimentary canal is subject to the formation of congenital, acquired, true, and false diverticula. The rare pharyngeal pockets which connect with branchial cysts are to be noted. Another equally rare type is found at the entrance of the trachea, possibly atavistic remains from the branchial pouch in some monkeys. Diverticula of the esophagus are not uncommon and, when small, are frequently overlooked. In advanced cases, when the bougie no longer passes the obstruction and the patient is suffering from starvation, they are quite often believed to be malignant. In some cases the true nature of the condition is discovered only when life has been prolonged, by the aid of gastrostomy, beyond the period prognosticated.

---

* Read in the Section on Surgery of the American Medical Association, at the Sixty-third Annual Session, held at Atlantic City, June, 1912. Reprinted from the "Jour. Amer. Med. Assoc.," July 22, 1912, vol. lix, pp. 260–264.

In 1840 Rokitansky[1] described two forms of esophageal diverticula, the pulsion or pressure variety, which is most commonly seen, and the traction variety in the middle third of the esophagus, caused by peri-esophageal inflammation usually developing from inflammation in the glands about the tracheal bifurcation. This variety seldom causes symptoms, but may be increased in size by coughing.

The condition usually develops on the posterior wall at about the level of the cricoid cartilage. The diverticula vary greatly in size from that of a walnut to a large sac extending into the chest, capable of holding a pint or more of fluid. These latter, because of traction, are more of the esophageal form. The term "pharyngo-esophageal" diverticulum might be applied to many of this variety. Diverticula of any form occur but rarely in the lower third of the esophagus. They are found only at postmortem.

Opposite the cricoid cartilage there is often a weak or muscle-missing space, called the Lannier-Hackerman area. Here the mucosa, under favorable conditions, may be pushed out from within and, once begun, the tendency is to increase. Thus the sac becomes a prolongation of the proximal gullet, while the lower esophagus opens out of the anterior wall of the sac. Arthur Keith[2] states that the superior pharyngeal muscles act as a force-pump, while the lower constrictor muscles act as an obstruction. This condition is seldom seen before middle life.

Aided by the radiogram following the liquid bismuth, and by the Plummer[3] test, diagnosis of diverticulum of the esophagus is no longer difficult. The Plummer test consists in having the patient swallow one end of a few yards of silk twist, such as is used by Mixter in treating esophageal stricture. When enough of this thread has passed through the stomach and into the intestine to stand some traction, the outer end is threaded through a perforated esophageal bulb-pointed probe, which slides readily down into the diverticulum, the thread being held loosely. The thread is then tightened, and the probe is elevated from the bottom of the pouch to the level of the true esophageal opening and pushed down into

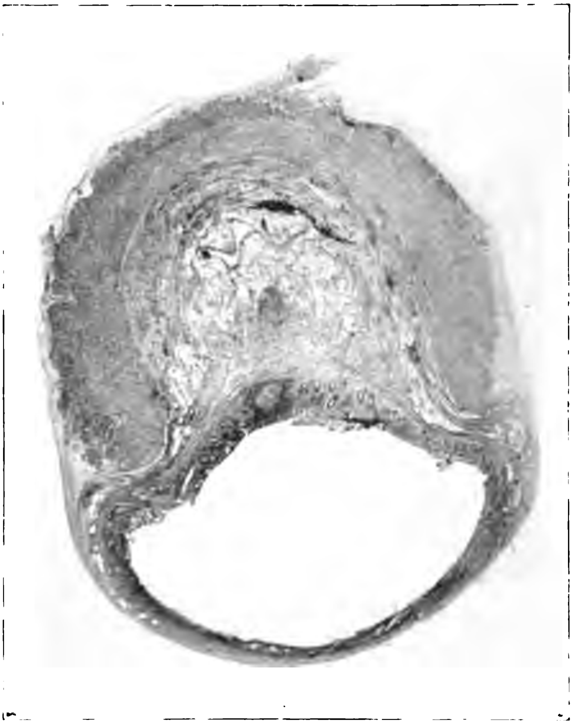


Fig. 39.—Section showing the coats and character of a diverticulum of the appendix.

the stomach, thus measuring the depth of the diverticulum as well as its presence.

Extirpation at one operation effects a cure when the sac is small. Invagination of the sac into the esophagus, as is sometimes done, is not recommended. Operation in two stages is preferred for large sacs extending into the mediastinum: (1) The sac is drawn out of the thorax into the neck; (2) after granulation has closed the cellular space, the sac is removed.

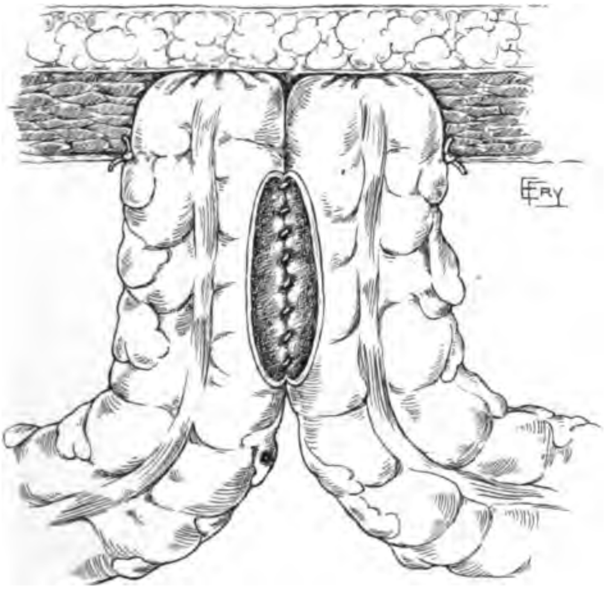


Fig. 40.—Bloodgood's preparation, colostomy if needed.

From January 1, 1902, to January 1, 1912, 13 cases of diverticula of the esophagus were diagnosticated in the clinic at St. Mary's Hospital. Ten of them were operated on and cured.

Diverticula of the stomach occur more commonly in the lower animals, namely, the pig family. They are found near the cardiac orifice. But few cases are reported as having been found in man. Keith reports two in which the diverticula were located near the cardiac opening. Falconer[4] reports one found in the pyloric end of the stomach which contained pancreatic tissue. One case was observed in our clinic. This was a woman, aged thirty-five, with irregular bowel symptoms and a tumor of the anterior wall of the stomach 2 inches from the pylorus. In the outer half of the diverticulum, which was 1½ inches in length, was a well-marked carcinoma. The tumor was excised and a gastrojejunostomy made, neither diverticulum nor malignancy being recognized until after the excision.

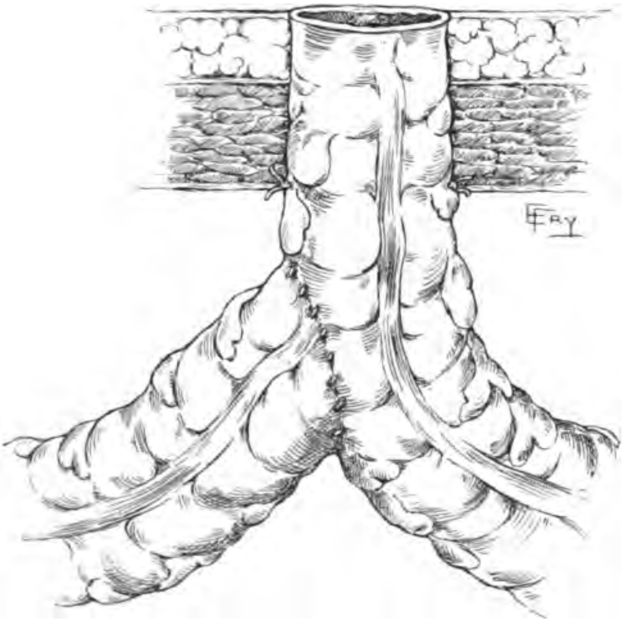


Fig. 41.—Temporary colostomy.

Diverticulum of the intestine, which has been described for more than one hundred years as an anatomic rarity, is now recognized as an occasional cause of serious disability and danger. The diverticula are often multiple. As many as 400 have been found in one individual. Telling,[5] who tabulated 105 collected cases, shows that they occur as often in men as in women, and that about 60 per cent. of his collection give clinical symptoms. Others, however, show that in approximately one-third of the autopsies on the middle-aged and the old diverticula are to be found. The greater number, then, give no symptoms.

No cases have been reported as giving typical symptoms of this condition in the duodenum during life. Clogg[6] and Alexis Thompson[7] report cases similar to the one found in the stomach by Falconer, that is, sacs on the duodenum containing pancreatic tissue. Accessory pancreatic tissue had been noted also in Meckel's diverticulum. Pressure-diverticula may appear late in life in the wall of the duodenum at about the location of the common duct. Visceroptosis is usually noted in the cases described.

Cases have been observed in our clinic of inflammatory pouches connected with the gall-bladder and extending, at times, to the liver, but more frequently they were found on the surface of the fundus of the gall-bladder. Some of these diverticula are apparently of congenital origin.

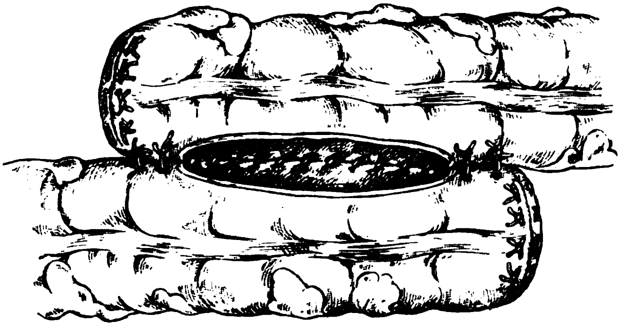


Fig. 42.—Lateral anastomosis.

The common and hepatic ducts of the liver are subject to diverticula in the presence of obstruction to the delivery of bile into the intestine. Such pockets often contain a large number of stones. Removing the stones and probing through the papilla into the intestine, with drainage of the hepatic duct through the opening in the common duct (after Robson's method), has proved very effectual in giving relief; one does not know, however, the after-condition of the sac, and we know that reformation of stone in the common duct is proportionately more frequent than in the gall-bladder.

The jejunum and ileum are both subject to the formation of diverticula, which are found along the mesenteric line of the intestine. One reported case[8] showed many sacs projecting into the mesentery between the peritoneal folds, the smaller ones showing a vessel at the end of the pocket which evidently had much to do with their origin. In a few instances only has any intestinal content or other foreign material been found in this type. One such has recently been reported by Walker.[9] Keith believes that they are found only in the pockets in which the entrance is smaller than the sac. They are composed of cholesterin or carbonate of lime.

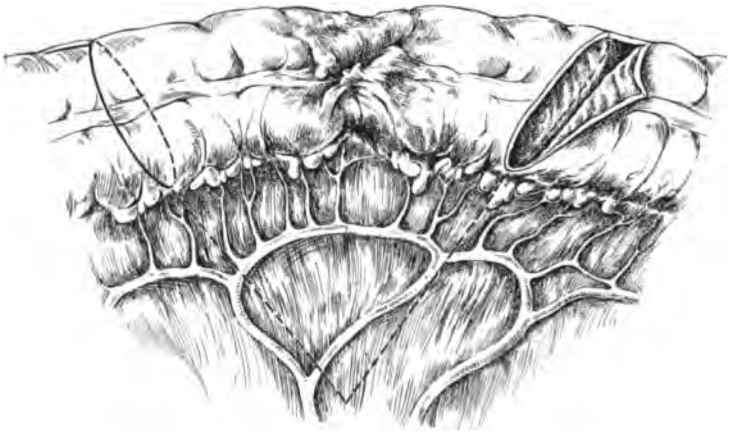


Fig. 43.—Incision to enlarge the lumen.

Meckel's diverticulum has been discussed in a previous report from our clinic[10] in which 15 cases were collected from 10,600 routine abdominal operations.

Diverticula of the large bowel are common. Even the appendix (Fig. 39) may have one of its own—a diverticulum within a diverticulum. Seventeen diverticula have been discovered in appendices removed at operation in our clinic. It is quite possible that the so-called double appendices which are sometimes reported may be nearby projecting diverticula which develop into appendices epiploicæ.

In one of our cases a tumor was removed from the surface of the transverse colon without resection. The symptoms were of tumor and local peritonitis. Dissection of the excised tumor revealed a diverticulum with a great, inflammatory, fatty mass developing through the chronic peridiverticulitis. The patient was afforded only partial relief, since contraction followed the operation, and three months later, at a second operation, this portion of the colon was excised with resultant cure. Deposits of such character were observed by Virchow[11] in 1853, and were described as isolated, circumscribed, adherent peritonitis of the colon. From this description, which so accurately pictures peridiverticulitis, it would appear that the condition is frequently overlooked. A very careful search of the mucosa with the probe in these cases will usually reveal the true condition.

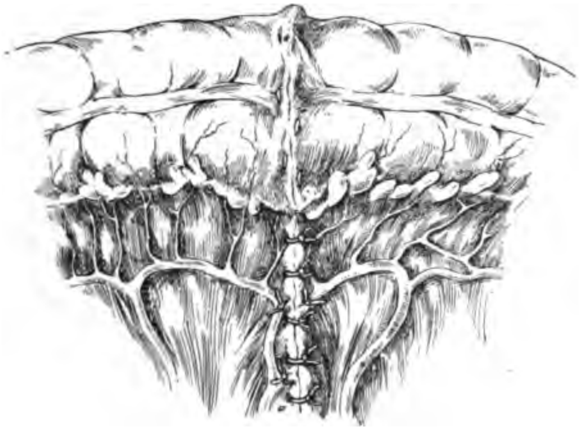


Fig. 44.—Resection to enlarge point of union of bowel.

In the sigmoid, the natural fecal carrier of the colon, are found the greatest number of diverticula giving symptoms. In some cases colostomies have been done for the relief of obstruction supposed to be due to cancer of the bowel, and the patient apparently cured, or life has been prolonged so as to preclude the diagnosis of malignancy. The natural inference in some of these cases is that the tumor was the result of the peridiverticulitis.

In our series of 27 cases of diverticulitis of the large bowel we have 2 in the rectum and 1 in the anal ring. Five additional cases were observed in operating for other conditions, but no pathologic specimens were obtained. One case was observed in operating for the removal of a large, double intraligamentary

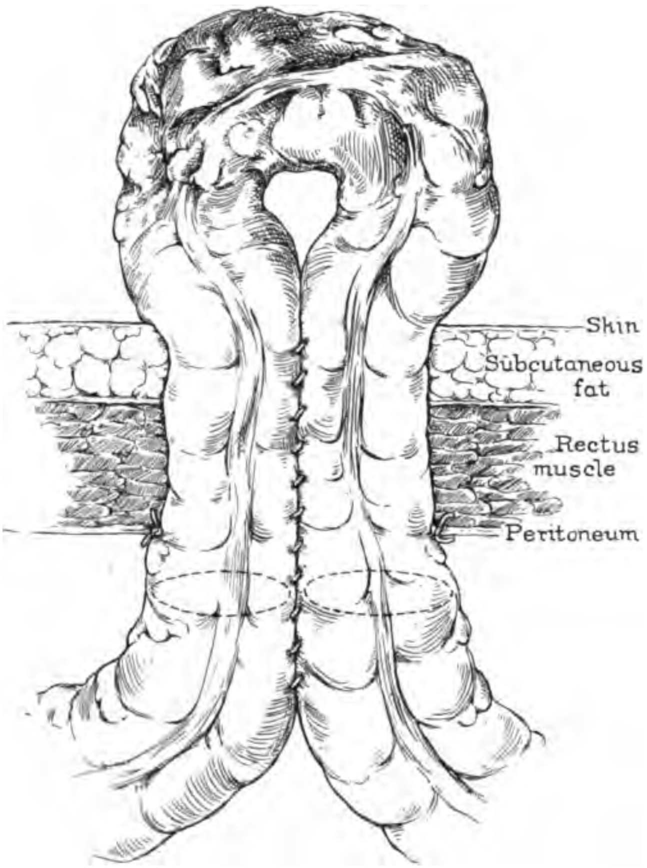


Fig. 45.—Tumor lifted out of abdomen, loops of bowel sutured into wound (Mikulicz operation).

cyst. This was a diverticulum of the cecum, located on the outer side, 1½ inches from the base of the appendix. It was 1½ inches long, and about the size of the little finger. In the case of non-malignant diverticulitis of the rectum the true diagnosis was made when the tumor was dissected after removal. Undoubtedly cases like this may form some of the perirectal abscesses which open near the anus on the skin and fail to become cured after repeated operations because the high internal opening of the fistula pre-

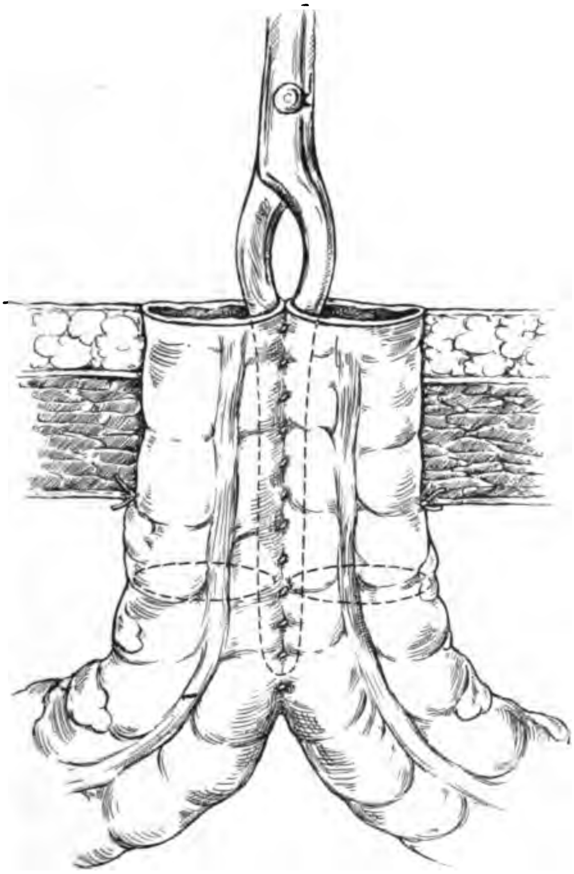


Fig. 46.—Tumor amputated, forceps passed into ends of bowel and clamped (Mikulicz operation).

serves the mucous lining of a portion of its wall. Again, these abscesses rupture into the bladder from the high rectal or sigmoid location. In this emergency gas will be noted passing with the urine. Harrison Cripps[12] estimates that the great majority of these fistulous conditions in the bladder are inflammatory and not malignant.

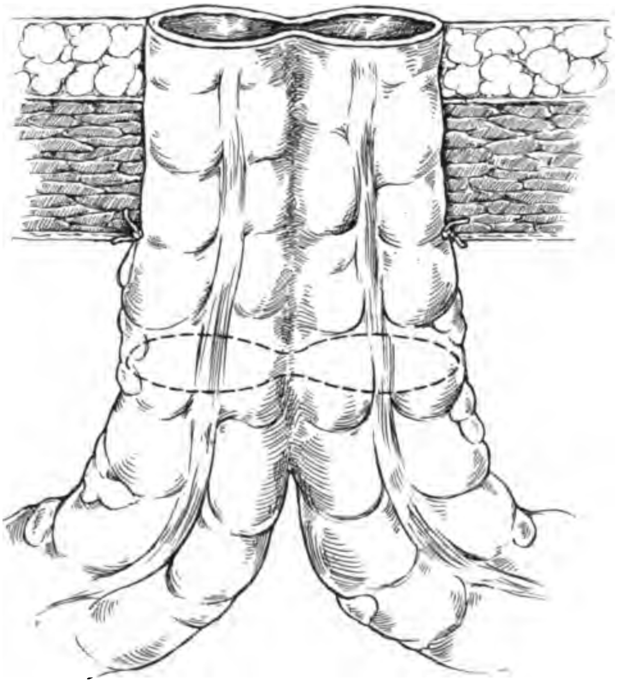


Fig. 47.—Anastomosis completed (Mikulicz operation).

Diverticula of the large intestine, similar to acquired hernias in other organs, are generally considered the result of pressure. A few of them are probably true diverticula possessing all the coats of the bowel at their origin, and in the early stage may be barely macroscopic. It is believed that many cases of diverticula originate in openings which have become dilated by congestion of the vessels passing into the bowel on the mesentery, or on the sides of the bowel at the site of the epiploic tags. This phenomenon is similar to the small ventral supraumbilical hernia which originates in openings in the aponeurosis and which has been sawed by the vessels and nerves. A congenital local defect, with pressure in early life, probably has considerable influence on this development. The circular muscle-fibers give way first, later the longitudinal fibers, and many cases show a rambling between of the diverticula. Wilson[13] has shown that in many cases the condition is one of peridiverticulitis rather than of diverticulitis alone. There may also be diverticulitis of mucosa with peridiverticulitis. Inflammation may be painless, especially in the early stage. In fact, the condition is difficult to diagnose until the subacute inflammation develops a mass of tissue at the site of the diverticulum on the outer surface of the bowel. This inflammation of the intestine then gives symptoms of a secondary nature. The patient has attacks of pain, gas, distention, or more or less obstruction with local peritonitis. Because the mucosa is not ulcerated there is little to be observed in the intestinal contents, blood or mucus and diarrhea being the exceptions.

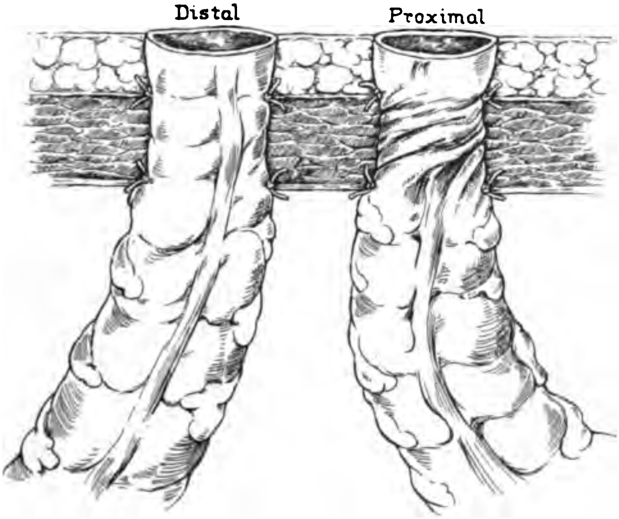


Fig. 48.—Gersuny twist for control of bowel.

Diverticulum of the large bowel is to be differentiated from tuberculosis, cancer, specific disease, left-sided appendicitis, as well as failure of the colon to rotate. In many instances no previous trouble or complaint existed; consequently the condition was not suspected before operation. We have made a probable diagnosis in seven cases. If a tumor be noted during or after an attack of obstruction, with some local peritonitis, the condition is often considered malignant, yet the lack of common symptoms of that disease makes diverticulum a possible factor. On the other hand, on exploration the peculiar contracted inflammatory appearance of the tumor makes a clinical diagnosis of cancer appear probable in a considerable number of cases which can be determined only by section on the microscope after removal. Peridiverticulitis with symptoms from infection with or without perforation or obstruction occurs one-seventh as frequently as cancer of the sigmoid.

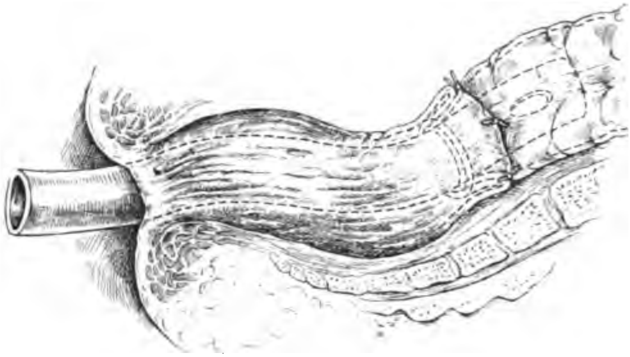


Fig. 49.—Anastomosis by tube, drainage.

In 7 of our 27 cases we found cancer grafted on diverticulitis of the large intestine. This was also the case in the diverticulum of the stomach and in several cases of diverticula at the base of the bladder, associated with small stones. It may be noted here that MacCarty and McGrath[14] have shown, from a study of 5000 appendectomies, that cancer of the appendix appears once in every 225 cases of chronic appendicitis. Therefore, diverticula affecting the intestine should be looked on as a potential source of cancer.

OPERATION

Anastomosis of the small bowel into the large is probably the safest of all forms of anastomosis, as it delivers liquid contents into the drying bowel. The union of large bowel to large bowel is a more serious procedure. A resection with bowel-union, sometimes preceded by preliminary colostomy, is indicated in most cases, or the operation is made in the two-stage Mikulicz method, in which case the tumor is lifted out of the abdomen, the sides of the two loops of bowel are attached to each other for 4 inches within the abdomen, and sutured into the abdominal wound. After four days the tumor is amputated at the abdominal wall, the blades of a pair of heavy forceps are passed one into the proximal and one into the distal ends of the bowel and clamped tight. This procedure requires about five days to cut through by necrosis, thus opening one bowel into the other, permitting closure of the colostomy later. This is especially recommended in fleshy patients whose resistance to infection is likely to be reduced. Bloodgood's[15] method of side-to-side, ends-together anastomosis, with ends of the stump brought into the incision beneath the skin as a safety valve to be opened if desired, is an excellent operation. Methods of suture-union by telescoping and by the use of a long, large-diameter rubber tube passed into the proximal end of the bowel out of the distal intestine and anus are fairly safe, as the line of suture-union and the lower bowel are not subject to gas tension or contamination, all passing out of the tube from the proximal bowel.

Immediate examination of the complete specimen with frozen section, if necessary, is an advantage in such cases and may often change the principle of the operation which has been planned, by proving the absence or the presence of malignancy. The mortality from operation due to varied causes approximates 10 per cent.

REFERENCES

1. Rokitansky: "Handb. d. path. Anat.," 1861, vol. iii, p. 127.
2. Keith: "Brit. Med. Jour.," February 12, 1910, pp. 370–380.
3. Plummer: "Surg., Gyn., and Obst.," May, 1910, pp. 519–523; "Jour. Amer. Med. Assoc.," February 25, 1911, pp. 560–564.
4. Falconer: "Lancet," London, 1907, vol. i, p. 1296.
5. Telling: "Lancet," London, 1908, vol. i, pp. 843, 928.
6. Clogg: "Reports Soc. Study Dis. Chil.," 1908, vol. viii, p. 221.
7. Thompson: "Edinburgh Med. Jour.," 1908, vol. xxiii, p. 304.
8. Taylor and Lakin: "Lancet," London, February 19, 1910, pp. 495, 496.
9. Walker: "Jour. Amer. Med. Assoc.," April 20, 1912, p. 1190.
10. Balfour: "Jour. Minnesota Med. Assoc.," March 1, 1911, pp. 110–112.
11. Virchow: "Virchow's Arch. f. path. Anat.," vol. v, p. 1853.
12. Cripps, Harrison: "Cancer of the Rectum," 1907.
13. Wilson: "Ann. of Surg.," February, 1911, pp. 223–231.
14. MacCarty and McGrath: "Surg., Gyn., and Obst.," March, 1911, pp. 211–220.
15. Bloodgood: "Ann. of Surg.," February, 1909, pp. 161–182.

THE RADICAL OPERATION FOR THE RELIEF OF CANCER OF THE RECTUM AND RECTOSIGMOID*

WILLIAM J. MAYO

The true rectum lies between the levator ani muscle and the third sacral vertebra, and consists of the so-called second part of the rectum, as designated by American authors. It is derived from the cloaca, which is a highly differentiated part of the hindgut, and has 5 sources of blood-supply, all of which may be accompanied by lymphatics. The superior rectal and the middle hemorrhoidal arteries contribute the main blood-supply, however, and the lymphatics, which are scanty, usually pass along with these blood-vessels by way of the rectal, sacral, mesosigmoid, and internal iliac glands to the juxta-aortic group.

The rectum proper has no mesentery, and only a small part of its anterior surface is covered by peritoneum; it lies in the fatty supporting tissue inside the rectal fascia, between the genito-urinary organs ventrally and the sacrococcygeal framework dorsally. Carcinomas of the true rectum are covered by peritoneum ventrally to some extent in more than half the cases. The type is adenocarcinoma.

The so-called first portion of the rectum has been shown by Treves[1] and Jonnesco[2] to be the terminal portion of the sigmoid derived directly from the hindgut, and its lymphatics pass to the aortic group by way of the mesosigmoid, following its single source of blood-supply. All the growths in this situation are covered by peritoneum ventrally. The type is adenocarcinoma. Only 24 per cent. of rectal cancers lie completely below the peritoneum (Tuttle[3]).

---

* Read before the American Surgical Association, May 29, 1912. Reprinted from "Annals of Surgery," August, 1912, pp. 240–255.

The so-called third portion of the rectum is derived from the ectoderm or skin-fold, and its lymphatics drain into the inguinal and coccygeal glands, as well as upward into the rectal glands. The anal canal is about 1¼ inches in length, contains no glands, and is lined by pavement epithelium. This part is the primary source of malignant disease in about 6 per cent. of the cases of cancer of the rectum. The type is epithelioma.

In operating for cancer two important principles in technic are involved: (1) Complete removal of the local focus with such adjacent tissue as might possibly be affected, and (2) the removal, to as great an extent as possible, of the tributary lymph-nodes. To accomplish these objects in operating upon the true rectum for cancer means the removal of the entire organ, with such a destruction of the muscles and nerves as will probably render efforts at securing a controllable anus impossible. While a good result is occasionally obtained by drawing the sigmoid downward and passing it through the muscles of the anal canal from which the mucous membrane has been removed, such fortunate instances are rare. In most cases there results a preternatural anus at the normal situation, and this latter condition cannot be considered a restoration, but merely a sentimental attempt to place what amounts to colostomy at an unfortunate situation—the anal site. This is especially true if the muscles and nerves have been seriously damaged; in such cases an abdominal colostomy or a sacral anus will give as good or better results at a smaller risk. However, each case must be judged on its individual merits; an attempt to conserve function must not be allowed to result in failure to eradicate the disease.

Handley[4] has shown that carcinomatous implantation may be found in the bowel 6 inches above the visible expression of the disease. Fagge[5] has demonstrated, in 2 cases, an extension downward into the lymphatics of the anal canal, without *visible* involvement of the canal itself. In Fagge's opinion, with which I agree, the entire anal canal should be removed when the carcinoma has its origin in the rectal ampulla.

The necessity of a wide eradication of the disease with at least 6 inches of apparent sound bowel above and not less than 2 inches below, with all the surrounding fat and glands, usually means a permanent colostomy in some situation. The functional incapacity following the operation must be accepted by the patient as the price paid for the cure. Occasionally a case may be found early enough so that the disease can be removed locally with success. In 5 instances in the clinic in St. Mary's Hospital cancer of the rectum was discovered early enough to enable us to remove the focus by a purely local operation and no recurrence followed. In a few of our cases the strictly local nature of the disease seemed to justify a limited resection of the rectum with direct suture in continuity, but in the greater number of cases such operations cannot be considered, as they either subject the patient to an operation which is not radical and gives but a faint hope of cure or greatly increase the danger of sepsis from leakage.

Failure to remove the disease in an orderly manner, and not the natural tendencies of rectal cancer, is responsible for the pessimism of the profession toward the radical operation for removal of malignant growths in the rectum and rectosigmoid.

High-lying carcinomas of the rectum, in the so-called first portion of the rectum, in the large majority of cases can be considered to have their origin in the terminal sigmoid. Since, in most of these cases, the rectum is involved in its upper portion, and in all it must be removed to a great extent, it is wise to consider all high rectal and terminal sigmoid growths in one group as rectosigmoid. They form a very considerable percentage of carcinomas of the rectum, and when localized, are extremely favorable for curative operation.

In a limited number of cases the sigmoid can be anastomosed to the lower rectum by the tube method after resection, but in a considerable percentage, and perhaps the majority, the disease involves the rectum extensively and an operation cannot be considered complete which does not remove the entire rectum and lower sigmoid.

Colostomy through the left rectus muscle, as advocated by

Lilienthal,[6] gives good functional results, and, as contrasted with a preternatural anus in any other situation, is to be preferred. A colostomy in the rectus muscle can be controlled by a simple abdominal binder—the weight of the abdomen in the bandage making the gentle pressure that is necessary for closure. The rectus muscle is as controllable as the biceps, and temporary voluntary control is often obtained, even against gas and fluids. Iliac colostomy, on the contrary, is placed in a situation where pressure must be brought by a pad or some other artificial means; the control may be efficient, but generally does not bear comparison with that obtained when the opening is made through the rectus muscle.

If the colostomy be done as a primary operation, to be followed later by radical removal of the disease, it allows thorough evacuation of the bowels and careful cleansing of the distal fragment before undertaking the second operation. When it is considered that 90 per cent. of the deaths following operation are due to sepsis,[7] the importance of this step cannot be overestimated.

A sacral anus is fairly well controlled by proper apparatus, and the average patient is, for sentimental reasons, better pleased with a colostomy behind, as that after all is what a sacral anus amounts to, than with a colostomy in front.

Operability.—Carcinoma of the rectum and rectosigmoid remains a local condition until a late stage. I have never seen a case in which a locally removable carcinoma in this situation has been inoperable because of glandular metastases alone. We have not infrequently seen cases which were locally removable and fairly free from glandular metastasis, but in which the liver was involved in embolic carcinoma. This is especially true in the young. In a few instances we have seen peritoneal metastases and implantation carcinoma in the mucous membrane, both above and below the primary seat of the disease, in cases locally operable.

In many cases rectal examination will not determine whether or not the disease be locally removable, and, since it is essential to know that there are no irremovable metastases in the abdominal cavity, an intraperitoneal exploration should constitute the first step in operating on cancer of the true rectum and rectosigmoid. Not until this is done and the disease viewed from above can the question of rectal conservation be settled. This, however, should not be considered an arbitrary law. In the very obese, the cachectic, and those in poor physical condition from general diseases a single operation by the perineal or sacral route may be preferred to a method which requires two operations, although an occasional patient may be operated on radically who has abdominal metastasis unknown to the operator because unexplored.

Inoperability is usually due to extension anteriorly to the region of the genito-urinary organs. When the mucous membrane of the bladder is affected and there is mechanic difficulty in micturition, an operation is not only futile, but has also considerable mortality.

Involvement of the peritoneum and muscular coats of the bladder is not unfavorable to operation, and on a number of occasions we have removed a part of the bladder-wall down to the mucosa, with good results. Involvement by direct extension to the uterus does not mean inoperability. If necessary, the uterus with both ovaries and tubes can be removed at the same time. This was done in five of our cases. Carcinoma implanted upon the ovaries and and pelvic peritoneum, however, is much less favorable for operation. The very fact that these carcinomatous cells have been loose in the peritoneal cavity means that other organs may be involved, although, on account of the rapidity of the progress of the disease in the ovaries, they are the only organs manifestly affected at the time.

The prostate and seminal vesicles, when involved in the carcinoma, can easily be removed to such an extent as may be necessary, but the prospect of cure is poor. In one patient we removed an inch of the posterior urethra and a piece of the bladder, followed by direct suture; the prostate and right seminal vesicle were also removed. The patient recovered with control of the bladder. We have dissected the ureters from the bladder to the brim of the pelvis in a number of cases, and after covering them with vaselin, have allowed them to drop back into position.

Ureteral fistula has not followed in any of these cases. We have found that if the ureters are thoroughly covered with vaselin after separation and denudation, both in this operation and the complete abdominal hysterectomy of Wertheim, ureteral fistula has not occurred. Gauze should not be allowed to come in contact with the denuded ureter in the drainage. It has been said that few cases of cancer of the rectum are operable beyond nine months after the beginning of the symptoms. This is an error. A number of our cases in which the symptoms had existed more than two years proved to be in excellent condition for operation. Much of the reputation of colostomy as a palliative operation depends on the fact that cancer of the rectum is a slow process and long remains a local disease. These extensive operations, however, can be made with a justifiable mortality only where a preliminary colostomy has been done and the rectal fragment has been carefully cleansed.

Two years ago I presented a report of 120 cases of resection of the rectum.[7] Since then we (C. H. and W. J. Mayo) have operated on 71 additional cases. I wish briefly to review these with special reference to the operative methods and immediate mortality, reserving the question of ultimate results for a future report.

For convenience, the 71 cases submitted to radical operation from January 1, 1910, at which time the former statistics ended, to April 1, 1912, have been divided into two series:

(1) Operations through a perineal or posterior incision in a single stage; (2) operations through the abdomen or abdominal combined with a perineal or sacral incision in one or two stages. Each will be discussed separately.

1. Operations Through the Perineum or a Posterior Sacral Incision in a Single Stage.

—In this series there were 27 cases, with 2 deaths (7 per cent.).

(*a*) *Local Operations.*—It is the rule in our clinic that the rectum shall be examined digitally in practically all of the cases in which an abdominal or pelvic complaint exists, whether or not there be rectal symptoms. Thus we have, on 5 occasions, as previously mentioned (2 in this group of 71), discovered carcinoma as a small localized mass from the size of a bean to that of a filbert, in patients with few or no rectal symptoms. Two of these were in degenerating polyps. Under an anesthetic and after careful dilatation of the sphincter a clamp was placed in such a manner as to bring up the growth with a wide zone of normal mucous membrane. The carcinoma was cut away with scissors and the base slowly seared with a hot iron. In 1 case it was necessary to use a catgut suture in addition. These 5 patients have all remained well.

(*b*) *Cripps' Perineal Resection.*—In this group there were 5 cases with no deaths. All involved the anal canal. The tumor, with a good margin of skin about the anus, the sphincters and a wide area of fat, the anal canal and a sufficient amount of the ampulla of the rectum were removed. The rectum above was not loosened from its bed and no attempt was made to unite the skin to the stump of the rectum. With a little care in the use of bougies in the third and fourth week, to prevent contracture, the functional results were excellent. In two of these cases the inguinal glands were removed at the same time. Undoubtedly it is good practice to remove the inguinal glands in all of these cases.

(*c*) *Quénu-Tuttle Perineal Resection.*—In this group there were 12 cases with 1 death (8⅓ per cent.). This operation is most properly applied in women. It consists, with or without removal of the coccyx, of a rapid dissection of the entire rectum from the hollow of the sacrum through a posterior straight incision. The dissection is extended anteriorly until the peritoneal cavity is opened. A gauze pad is placed inside the peritoneal cavity. The entire rectum is separated from its lateral attachments, which are caught in the forceps much as are the broad ligaments in vaginal hysterectomy. Compression in the clamps for a few minutes, as pointed out by Bevan,[8] stops all tendency to bleeding from the hemorrhoidal vessels. As a rule, the entire mass can now be drawn through the incision with little difficulty.

The superior rectal artery is tied and the proximal stump of sigmoid cauterized with the Paquelin cautery. In many cases the anal canal can be saved, and after stripping of its mucous membrane the lower end of the tied sigmoid is drawn through and fastened. We have followed Peck's[9] advice, leaving the stump closed for from twenty-four to seventy-two hours before opening, and have obtained primary union in some cases. The patient is operated in the perineal position. This operation is indicated in very fleshy, elderly females in whom any kind of an abdominal operation would be fraught with great difficulty and danger, and in patients who are cachectic and anemic. Of these 12 cases, 2 were extremely anemic from continued loss of blood, 1 having 22 per cent. hemoglobin and the other 28 per cent. Both made good recoveries. In the male this method does not give a sufficient view of the genito-urinary apparatus. In the female the bladder is protected by the uterus and vagina.

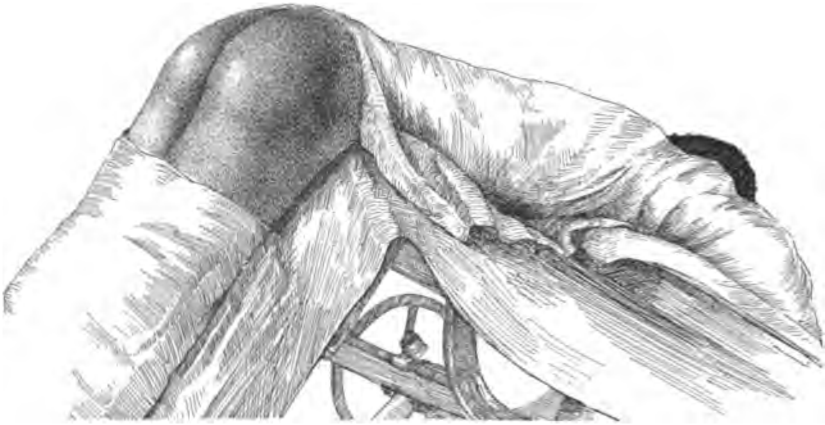


Fig. 50.—Patient in reverse Trendelenburg posture for excision of the rectum.

(*d*) *Posterior Resection of the Kraske Type* (Fig. 50).—Eight primary operations were made by the posterior route, with 1 death, and 30 secondary to an abdominal operation, with 4 deaths. This method as a primary one-stage operation was chosen in fleshy males and in several females with strictly localized growths well above the anal canal. In 5 the tied end of the sigmoid was drawn down through the anal canal, which was stripped of its mucous membrane. In 3 cases the functional results were good. In 2 the end of the sigmoid sloughed and separated from the

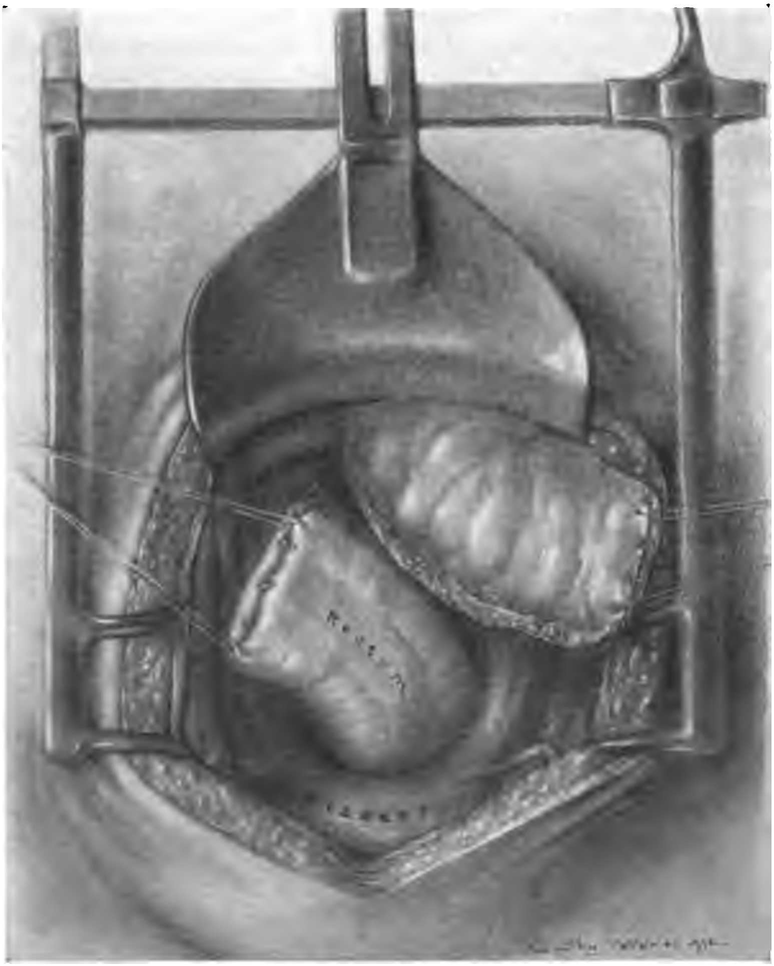


Fig. 51.—First stage of abdominosacral operation, division of lower sigmoid and permanent colostomy. Second stage, removal of entire rectum and sigmoid to point of division, from behind.

muscles and the functional results were poor. In 1, a rectosigmoid growth, direct suture in continuity was made over a tube. A sacral anus was made in the remaining 2 cases.

In the posterior operation we have followed the plan of putting the patient on the operating table in the reverse Trendelenburg posture (Fig. 50), closing the anus by suture, and making an incision in the posterior midline 8 or 9 inches in length from the upper sacrum to the anus. The coccyx and the fourth and fifth sacral vertebræ are removed, which gives a fairly good operative space (Fig. 51). The dissection is then made usually from below upward. It should be accurate and anatomic, exposing the posterior urethra, prostate, seminal vesicles, and posterior wall of the bladder in the male, the vagina and uterus in the female, and, as a rule, the ureters in both sexes. Hochenegg[10] has had a large experience in posterior resections for rectal cancer. I have recently had the pleasure of seeing Professor Hochenegg do his operation. In removing the fourth and fifth sacral vertebræ he makes the bone section slightly concave from below upward. He has no difficulty in removing growths which can be barely reached by the examining finger. In two-thirds of the cases operated on a sacral anus is made. Five hundred cases have been operated on in the Vienna clinic by the Hochenegg method, with a mortality of 18.9 per cent. and 20 per cent. of five-year cures. In his private work, Hochenegg has a mortality of a little less than 10 per cent.

2. ABDOMINAL AND ABDOMINAL COMBINED OPERATIONS IN ONE OR TWO STAGES.—This series contains 44 cases with 9 deaths.

(*a*) *Abdominal and Abdominoperineal Operations in One Stage.*—There were 14 cases, with 5 deaths, in this group:* The lower sigmoid and rectum were removed through the abdomen or abdomen and perineum at a single operation. An incision is made in the midline, suprapubically, sufficient to admit the hand for exploration. The patient is elevated into a sharp Trendelenburg position, and the incision is extended until it reaches from the umbilicus to the pubes. The sigmoid is drawn out and the abdominal cavity is carefully packed off with gauze. The sigmoid is clamped in 2 places at least 6 inches above the growth, firmly tied, and divided. The ends are sterilized with the actual cautery. The inferior mesenteric artery or the superior rectal, depending upon the point of division, is tied. Both ureters are identified and separated, the peritoneum rapidly divided, and the entire cavity of the sacrum quickly freed. The middle sacral artery will usually have to be tied, and the lateral sacral arteries should not be forgotten. These arteries have their origin from the posterior division of the internal iliac. The inferior pass down on the face of the sacrum and enter the lower sacral foramina. If roughly handled, unpleasant bleeding may continue from the foramina and may be difficult to check. The middle hemorrhoidals are caught and crushed in clamps. By leaving the clamps on for a few minutes they can be removed and bleeding will seldom follow. It is easy to separate the lower sigmoid and rectum down to the levator ani muscle. The technic may then be varied. When the patients were in poor condition, we have on several occasions put an angular clamp across the lower rectum at its deepest portion, then clamped the upper side, cut between, and sterilized the cut end which projected from the deep clamp with the actual cautery. The clamps were left on, the handles projecting from the abdominal incision. The rectal space was packed with iodoform gauze which was brought out with the handle of the forceps. The wrist of a rubber glove was drawn over this down as far as the peritoneum of the bottom of Douglas' pouch, which was partly closed by sutures. The proximal end of the sigmoid was brought out as a permanent colostomy through a stab wound in the left rectus muscle and attached to the peritoneum on the inside by several sutures. Three out of 4 cases treated in this way recovered. They were advanced cases and the operation severe. In the remainder of this group the operation was completed through the perineum, removing the rectum from below. In 4 the end of the sigmoid was brought down through the anal canal, which was stripped of its mucous membrane. In 2 anastomosis of the rectosigmoid was done by the tube method[11] (Figs. 53, 54, and 55), which we have found

---

* The operative mortality is based on counting as a death from operation every case dying in the hospital without regard to cause of death or length of time thereafter. Some of these deaths occurred from exhaustion and general debility several weeks after operation.

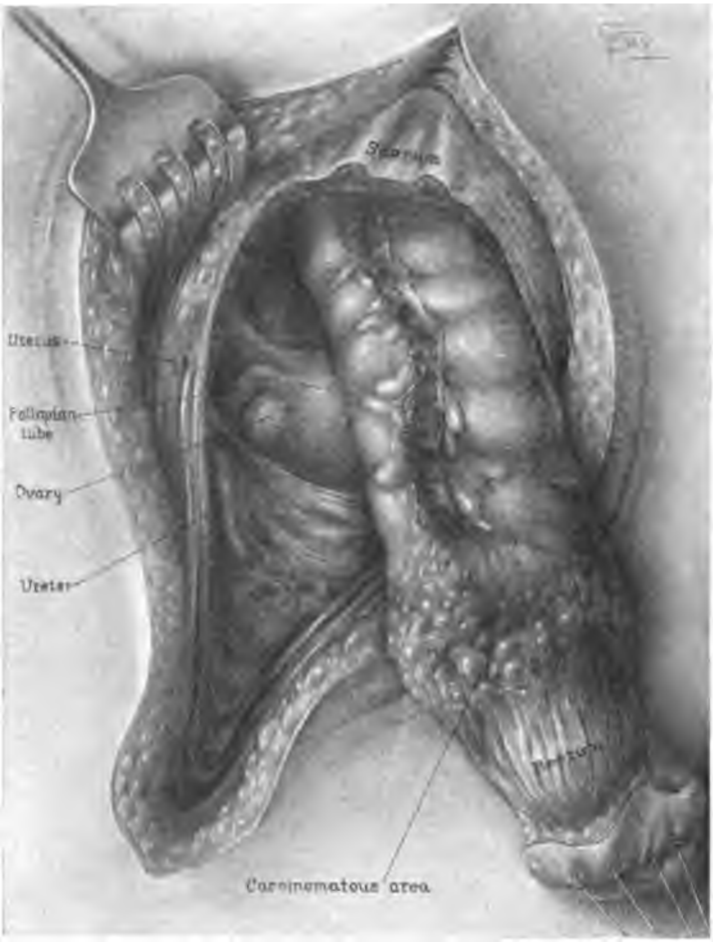


Fig. 52.—Posterior removal of rectum. Operation may be completed—(*a*) by a sacral anus; (*b*) by closure of end of sigmoid if secondary to abdominal colostomy; (*c*) by removal of entire rectum and sigmoid to point of division if sigmoid be divided.

useful for carcinoma of the sigmoid higher up. In 1 of these 2, a patient with marked obstruction, a preliminary lateral (iliac) colostomy was made, and a week later the rectosigmoid was removed through the abdomen and anastomosed by the tube method.

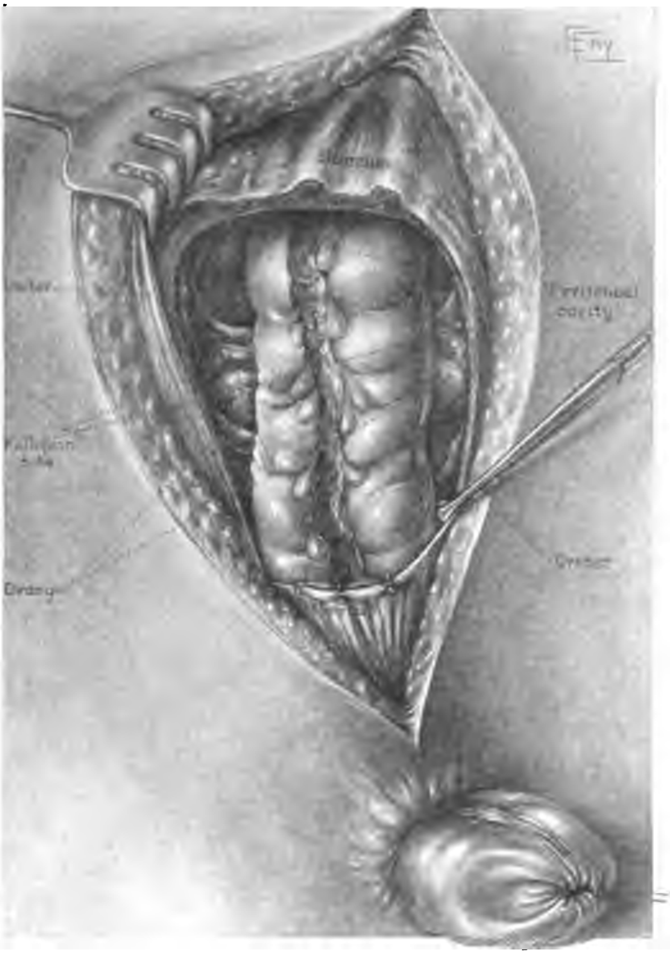


Fig. 53.—Terminal muscular rectum conserved. Mucous membrane removed and end of sigmoid pulled through and out of anus. End of sigmoid left closed temporarily by a purse-string suture.

The preliminary colostomy enabled cleansing of the lower fragment and diverted the feces until the rectosigmoid union was complete. The proximity of the colostomy was less embarrassing than might be expected at the second operation. The patient

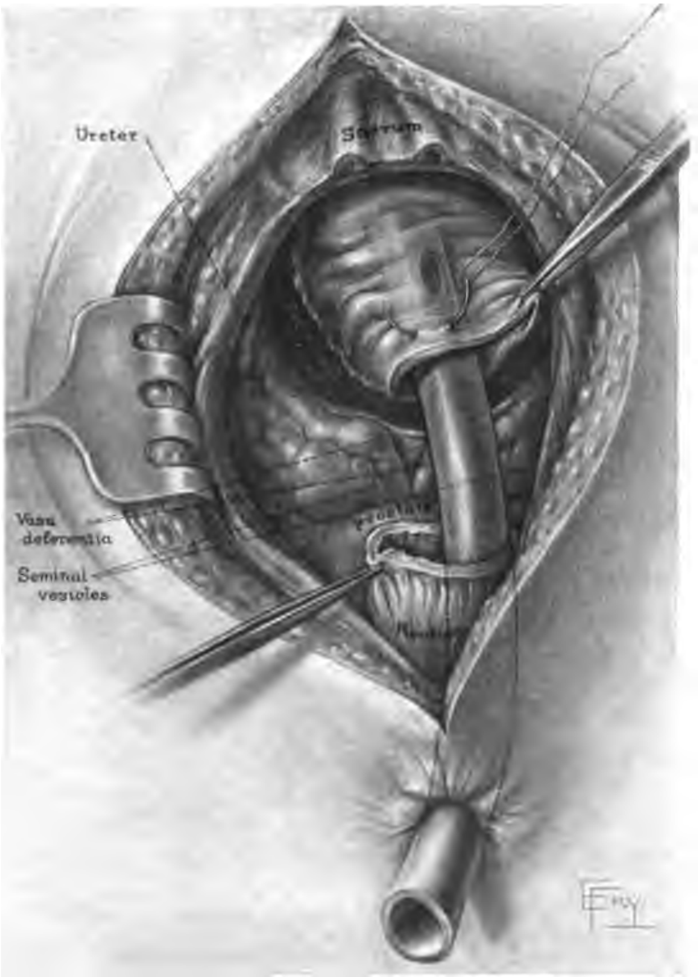


Fig. 54.—First stage of tube method of union of sigmoid to terminal muscular rectum, by posterior route. Rubber tube fastened to sigmoid by catgut suture, to be followed by direct mucomucous suture and finally by invagination and suture.

recovered. This method has merit when the true rectum is intact, and had we practised it in some of the cases that resulted fatally, I believe they might have been saved. In the remaining cases a permanent colostomy was done, the peritoneum being closed across the bottom of the pelvis as well as possible after

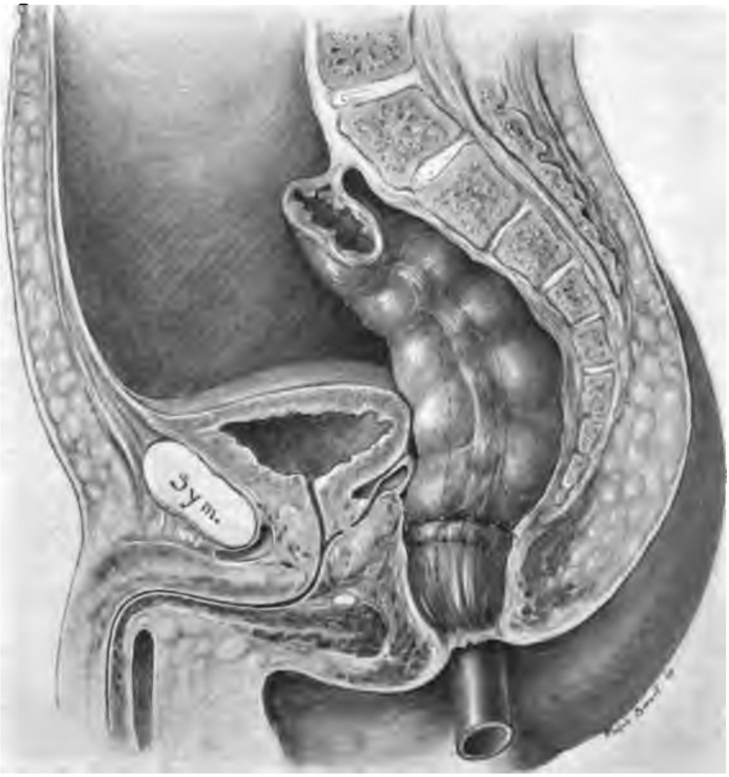


Fig. 55.—Sagittal section showing union of sigmoid and lower rectum. Completion of tube method.

packing the cavity with iodoform gauze, and bringing the ends out through the perineal incision.

(*b*) *Preliminary Colostomy with Secondary Posterior Resection.*—Thirty operations with 4 deaths (13 per cent.). There were a number of cases in this group in which acute, subacute, or chronic obstruction existed, and the majority, because of adipose tissue, cardiovascular changes, nephritis, etc., were poor surgical risks.

OPERATION

First Stage.—An incision is made in the left rectus muscle and the abdomen carefully explored. A colostomy through the incision is then performed by the Lilienthal method. After union is complete, daily irrigation of the lower fragment is begun, washing both from the colostomy through the anus and from the anus upward until the lower segment is clean. The bowels are evacuated on the fifth or sixth day with castor oil.

Second Stage.—Seven to twelve days following the first operation the entire rectum and rectosigmoid are removed from behind by the method described in *d*, series 1 (Fig. 51). The end of the sigmoid is closed completely by suture and left as an appendage to the colostomy from which mucus can escape. This method has two commendable features: (1) The relief of the obstruction; and (2) careful preliminary cleansing of the part to be resected. The mortality was relatively low, and the prospects of permanent cure as good as in any other group of cases. The logic of results points to this method as the one of choice in the majority of cases of high rectal and rectosigmoidal growths, but the last word is still to be said on this subject.

When the growth extends high on the lower sigmoid, the following variation in technic can be made: A midline incision is made suprapubically, the exploration completed, and the sigmoid brought up and divided between two ligatures and both ends sterilized (Fig. 52). The distal end is invaginated into the bowel with a purse-string suture, and the superior rectal artery tied. The mesosigmoid is divided above the promontory of the sacrum, the peritoneum divided on each side as far as the bottom of Douglas' pouch, and the fat and glands separated from their posterior attachments to this point only. The distal end of the sigmoid with the attached fat and glands is depressed and the peritoneum closed down and over the top of the mass. The anterior peritoneal attachments to the bladder and the lateral attachments of the rectum and lower sigmoid are not disturbed because the main blood supply through the superior rectal vessel has already been cut off. The end of the proximal sigmoid is brought out through the middle of the left rectus muscle as a permanent colostomy. A tube must be inserted into the lower fragment through the natural anus to carry off the discharges and to enable cleansing by gentle irrigation. On the fifth or sixth day the bowels are thoroughly emptied by means of castor oil On the sixth or seventh day a complete posterior resection is made, and the entire fragment from the anus to the point of previous section of the sigmoid is removed from behind, as described in *d*, series 1. The patient should be kept on his side after the sacral operation, and not on his back. This is an excellent method, but has an increased mortality over the method first described. It should not be practised in the very obese, nor in those with obstruction. We had one patient die several days following the colostomy from perforation of the lower fragment. We had no deaths from preliminary colostomy as usually performed.

In several instances the patient objected so seriously to a permanent colostomy that a lateral colostomy was made at the first operation, sufficiently high on the sigmoid to permit later manipulation. At a second operation the end of the bowel was drawn through the anal canal, which must always be stripped of its mucous membrane, and, after union was complete, the colostomy was closed. Since this second variation in technic depends on conditions which cannot be known until the abdomen is opened, consent must be obtained to make a permanent colostomy if essential. This method promises most for the future, as it gives the best prospect of a complete restoration of the continuity of the alimentary canal and rectal function with a small risk.

We are encouraged in contrasting the histories of these 71 cases with those of the 120 cases previously reported. While no one operation can be applied to all cases, and while more or less incomplete operations are sometimes found necessary because of the condition of the patient, the last two years have witnessed wider extirpation and more extensive operations generally. These now include an important group of cases heretofore considered hopeless. The 2 most important factors in these results are, first, elimination by means of preliminary abdominal exploration of cases of abdominal metastasis which would otherwise be subjected to unavailing and dangerous operations, and, second, the acceptance of permanent colostomy, sacral or abdominal, as a necessary evil in the majority of cases.

In the 120 cases previously reported, the mortality was 16 per cent. In the present group of 71 cases the mortality is about the same (15.5 per cent.), due to the acceptance for operation of cases which previously would have been considered hopeless.

In contrasting the various methods of operation, it can be seen that the operations grouped under series 1 give the smallest mortality. In the elderly, in the very obese patient, and in poor surgical risks, operations in one stage through the perineum or posteriorly (sacral) should be practised. The sacral operations, either as a primary operation or as the second stage of the abdominosacral method, is the operation of choice for the actual removal of the rectum. The great advantage of this particular operation lies in the fact that the disease can be extirpated widely at a single operation if necessary. In over half of the 191 cases in our combined series this type of operation was performed as a primary operation or as the second stage of the abdominosacral method.

The abdominoperineal combined method, performed at a single operation, is perhaps the ideal method. In the 14 cases of this type herein reported there were 5 deaths. Miles[12] lost 17 out of 42 cases; Wallis[13] gives a mortality of 40 per cent.; Hartmann[14] lost 1 out of 4 cases, and Kraske[15] 4 out of 10 cases. I am confident that were this method applied to all cases the mortality would be reduced one-half. It must be taken into consideration that the 14 cases subjected to operation in this series could not be done in any other way and were otherwise hopeless. The upper rectum and lower sigmoid were involved nearly to the promontory of the sacrum. In all a complete dissection of both ureters was necessary. Four of the patients had been operated on previously and a colostomy made because they were considered hopeless. In 2 cases a loop of adherent small bowel was coincidentally resected, and in 2 the uterus was involved and removed. Are operations justifiable in carcinoma advanced to this degree? Our experience leads us to believe that they are—we have a number of five-year cures in the 26 cases of abdominal and abdomino-combined operations in one stage in the previous series of 120 cases reported in 1910.

The combined abdominosacral operation in two stages has much to commend it, and has a mortality of less than one-half that of the abdominoperineal combined operation in one stage. The ability to cleanse the lower fragment and the relief of obstruction which a preliminary colostomy makes possible are of the greatest importance. This method also permits the removal of tumors of the most extensive description from the rectum proper, a situation in which the abdominoperineal combined operation affords insufficient access. The rectum can be dissected by the sacral route with as much precision as in the cadaver, and it is a suitable procedure for practically all growths of the rectum and rectosigmoid. Its greatest advantage lies in the fact that if a temporary colostomy be made to divert the fecal current until satisfactory union of the upper and lower fragments has taken place, in suitable cases complete restoration of normal function can be confidently expected.

We are today operating on patients whom three years ago we would have considered entirely beyond the reach of surgery because experience has shown that cancer of the rectum long remains a local disease, and by block dissection cure can be obtained in a goodly percentage of cases.

RESECTION OF THE RECTUM AND RECTOSIGMOID

January 1, 1910, to April 1, 1912

Total number	71
Discharged	60
Died	11 (15.5 per cent.)

Posterior and Perineal Operations

	No. Cases	Discharged	Died	Mortality Per Cent.
Local operation	2	2	0	0
Harrison Cripps	5	5	0	0
Quénu-Tuttle	12	11	1	8⅓
Posterior (Kraske)	8	7	1	12.5
	27	25	2	7

ABDOMINAL OR ABDOMINAL COMBINED IN ONE OR TWO STAGES

	No. Cases	Discharged	Died	Mortality Per Cent.
Abdominal and abdominoperineal: single stage	14	9	5	35
Preliminary colostomy with secondary posterior operation in 2 stages	30	26	4	13
Total	44	35	9	20

REFERENCES

1. Treves: Quoted by Cunningham, "Text-book of Anatomy," second edition, p. 1085.
2. Jonnesco: *Ibid.*
3. Tuttle: "New York Med. Jour.," 1908, vol. lxxxviii, pp. 433–440; 496–504; 535–542; 584–590.
4. Handley: "London Lancet," January 14, 1911, pp. 230–232.
5. Fagge: "London Lancet," February 28, 1911, pp. 232, 233.
6. Lilienthal: "Annals of Surgery," 1910, vol. lii, pp. 384–387.
7. Mayo: "Annals of Surgery," June, 1910, pp. 855–863.
8. Bevan: "Annals of Surgery," 1910, vol. lii, p. 139.
9. Peck: "Annals of Surgery," 1910, vol. li, pp. 242–245.
10. Hochenegg: "Presse Médicale," October 10, 1908; also personal communication, May, 1912.
11. Balfour: "Annals of Surgery," February, 1910, pp. 239–241.
12. Miles: "Glasgow Med. Jour.," February, 1912.
13. Wallis: "London Lancet," January 28, 1911, p. 231.
14. Hartmann: "Annals of Surgery," 1909, vol. l, pp. 1091–1094.
15. Kraske: "Arch. f. klin. Chir.," vol. lxxx, p. 634; also "Verhandl. d. Deut. Gesellschaft f. Chir.," 1906, vol. xxxv, pp. 428–435.

HERNIA

THE DIAGNOSIS OF DIAPHRAGMATIC HERNIA*

H. Z. GIFFIN

In obtaining clinical histories from patients it is well to inquire as to former injury, much as one would ask about previous disease or operation. In this manner a clue may be obtained which will occasionally lead to eliciting data of vital importance in the diagnosis. This point is forced upon one's attention in reviewing the reported cases of diaphragmatic hernia. The history of trauma is important evidence, as will be shown later.

For a discussion of the embryology, anatomy, and pathology of diaphragmatic hernia and related conditions the reader is referred to articles by Sailer and Rhein, Strüppler, Königer, Beltz, Becker, and others. Further discussion on the diagnosis will be found as well. It will be impossible to give credit in the text to all authors whose papers have been reviewed. German clinicians have been very thorough in their study of diaphragmatic hernia, and we are indebted to them for most of our information. The fact that little has been written in English upon the differential diagnosis has led me to prepare this discussion.

Many diaphragmatic hernias are congenital, but most of these have been found in stillborn babes or in infants. Hernia occurs through the various normal apertures of the diaphragm. Hernia into the pericardial sac has been reported. Right-sided hernias have, as a rule, been small and have contained a small knob of liver. The stomach has been found in the right side of the chest in one instance. Nearly all diaphragmatic hernias, however, are left-sided, and the subject will, therefore, be reviewed from this standpoint. Most important for diagnosis are the congenital hernias of adults and traumatic hernias.

---

* Reprinted from "Annals of Surgery," March, 1912, pp. 388-397.

About 650 cases of diaphragmatic hernia have been reported. Strüppler collected 500 cases in 1901. One hundred and seven reported cases have been found since then, and, in addition, 41 references have been collected which the writer has been unable to confirm personally. Most of these were either congenital hernias of babes or symptomless hernias discovered at autopsy. It would seem that 15 cases were diagnosed correctly during life. It is safe to say, however, that many mistakes have been due to the fact that the physician was unprepared for the condition; that the symptoms and signs of diaphragmatic hernia were often quite clear, but were not elicited because of lack of familiarity with them. On the other hand, an occasional case has been reported in which all the refinements of Teutonic technic have failed to differentiate the condition.

The most important and difficult differentiation to make is that between diaphragmatic hernia and *elevation of the diaphragm* (*eventration*). "Eventration" of the diaphragm was applied by Petit in 1790 to the condition of chronic idiopathic unilateral elevation of the diaphragm described by him. About 20 cases have been reported in the literature. As Königer suggests, it is not a good term surgically. The surgeon understands by eventration the condition in which a large part of the abdominal viscera is outside the peritoneal cavity. In fact, the word eventration might well be applied to diaphragmatic hernia, but not to high position of the diaphragm. Elevation of the diaphragm would be a better term; it is concise and its meaning is clear.

Elevation of the diaphragm is not an operative condition. Diaphragmatic hernia is generally surgical. The importance of deciding between the two conditions is therefore increased. Cases of elevation have been diagnosed hernia and unnecessarily operated on.

The diagnosis can best be discussed in a consideration of—(1) The clinical symptoms; (2) the physical signs; and (3) the radiographic and fluoroscopic findings.

If a history of severe trauma be elicited,—a crushing injury to the lower thorax or upper abdomen, as would occur if a man were caught between buffers; a severe blow to the upper abdomen or lower thorax, as in being struck by a flying plank; a severe twist with consequent strain upon the organs of the upper abdomen and the diaphragm, as in being jerked suddenly from one position to another; a sudden doubling of the body with chest between knees, as in a sand or gravel slide; a penetration of tissues in the region of the diaphragm, as in a stab wound,—the existence of rupture of the diaphragm should be suspected. In the acute condition marked dyspnea with severe upper abdominal and left thoracic pains, possibly with symptoms of intestinal obstruction and hematemesis, completes the clinical picture.

Chronic cases of hernia, either congenital or traumatic, may give a less striking symptomatology and a history of much less severe injury. In this they approach the symptoms of elevation of the diaphragm, where abdominal pain, dyspnea, and vomiting, though less severe, may recur in attacks, and these may be worse after trauma without rupture being present. Elevation is generally a congenital condition. A prominent symptomatology may only follow trauma. Dyspnea, pain, indefinite gastric complaints may be of varying grades. Hematemesis has been reported. It is in these chronic cases then that the physical findings and radiographic and fluoroscopic study are more important.

Tympanitic percussion-note, distant breath-sounds, gurgling and tinkling sounds over the left lower chest, with hyperresonant note and normal or slightly altered sounds over the left upper chest, are common to both conditions. The heart is displaced to the right. In diaphragmatic hernia Litten's sign may be absent, and it has been suggested that the line of tympany may be less movable than in elevation. Dulness below tympany has been noted in diaphragmatic hernia, and is probably explained in one case on record by the presence of spleen and in another by omentum. After giving a Seidlitz powder the signs may be much clearer and expansion of the stomach upward is likely to be more decided in hernia. Filling the stomach with water will cause partial flatness in place of tympany. Air or water pumped into the colon will likewise affect the tympany in the chest if the colon be part of the hernia; if this finding be definite, it may be regarded as an important point in favor of hernia. Examination after changes in position may furnish some evidence.

In radiograms of either condition the most noticeable abnormality is the existence of a curved shadow-line with concavity downward on the left chest, and the problem is to determine whether this shadow-line represents stomach-wall, as in hernia, a high diaphragm, as in elevation, or both stomach-wall and diaphragm, as in elevation. (1) The shadow of elevation generally maintains a typical dome shape, whether it be low or high, or whether the radiograph be taken before or after distention of the stomach with CO_2. The shadow of hernia may vary in outline, may be irregular or incomplete. (2) In diaphragmatic hernia the mottled appearance of lung tissue is visible through the gas contained in the stomach. This is not noted in elevation of the diaphragm even after extreme distention. These two observations are the most important ones in the radiographic differential diagnosis. If two curved shadows be present, a radiographic or fluoroscopic examination after distention of the stomach should indicate which line is stomach and which diaphragm; if the lower line be stomach, it will move up against the diaphragmatic line, and the pyloric end of the stomach will then unfold; if the upper line be stomach, distention upward into the chest will be almost unlimited. If the bow-line shadow represent both diaphragm and stomach, distention will cause merely the above-mentioned unfolding of the pars pylorica.

The passage of stomach-tube or lead bougie with subsequent radiogram does not seem to have yielded much additional information. Estimation of the intragastric pressure during inspiration and expiration in the two conditions has been attempted, but the results are not clear.

A series of *x*-ray plates following a bismuth meal should add some confirmatory evidence. The stomach may thus be identified as an organ lying in high position. The colon is almost always

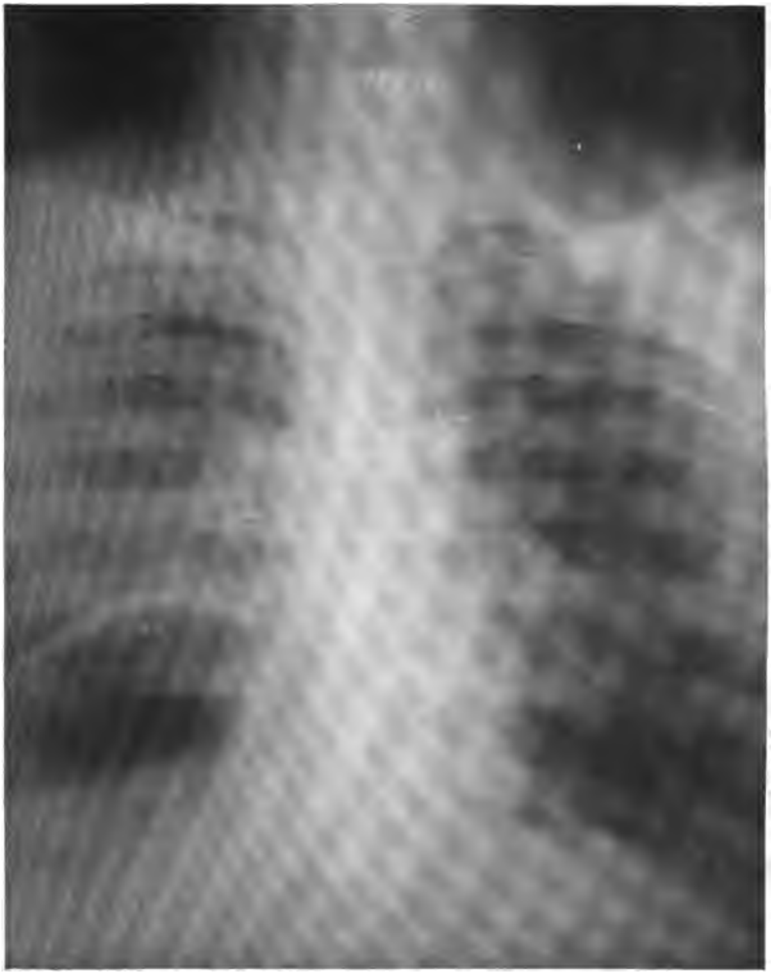


Fig. 56.

June 26, 1911: Case, diaphragmatic hernia, with the stereoscopic radiogram made of patient in the vertical position, the sternum next to the *x*-ray plate, care being taken to avoid any rotation of the spine on its long axis. The central focus corresponds to the level of the seventh dorsal vertebra.

We are viewing the thorax through from behind, therefore the right side of the print represents the right side of the thorax. These prints are facsimile reproductions of the original plates.

Note the position and outline of the pericardial shadow. The heart inclines strongly toward the right, its right border extending a greater distance to the right of the midsternal line than does the left border to the left of the spine.

Both hiluses are abnormally dense, the left being markedly enlarged. Both apices are clear and the pulmonary tissue is normal in all three right lobes and in the upper left lobe.

In the lower portion of the left thorax can be seen clearly a curved white line ot greatly increased density. The proximal end of this line is opposite the level of the spinal juncture of the eighth rib on the left side. From this point the line curves outward along the eighth interspace to the ninth rib. Between this line and the upper border of the tenth rib is seen a dark area of greatly decreased density, through which one can clearly distinguish branches from the lower pole of the left hilus. The costal portions of three ribs are also visible. The left margin of the pericardial shadow is not clearly defined.

Note the clear-cut outline of the dome of the diaphragm to the right of the spine and compare it with the faint, indistinct outline on the left of the spine, which is to be seen just below the tenth rib.

The unusual appearance of the lower portion of the left thorax attracted our attention and suggested strongly the probability of a hernia of the diaphragm. A study of the stereoscopic plates supported this suspicion, and it was deemed important to establish the position of the stomach, for it seemed likely that the dark shadow below the abnormally placed curved line was due to gas in the stomach. With this end in view an emulsion of subcarbonate of bismuth and acacia was given the patient by mouth and a second set of plates made immediately, the patient being in the vertical position. (See Fig. 57.)

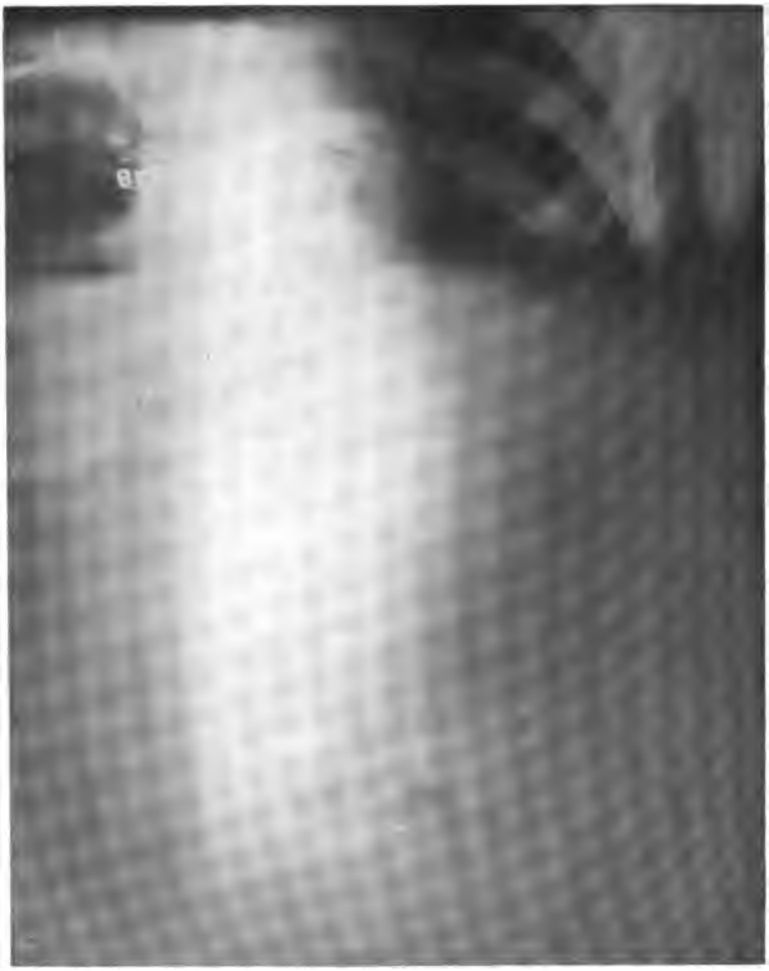


Fig. 57.

Radiographed immediately after the ingestion of bismuth subcarbonate emulsion. (Compare with Fig. 56.)

Note the line of demarcation between the white dense area and the dark area lying above it. The white shadow represents bismuth in the stomach, the upper border of the shadow representing the surface level of the emulsion. Above the bismuth is seen the gas-bubble of the stomach. This is limited above by the wall of the stomach, which we recognize as the curved line described in Fig. 56. Note the faint outline of the bismuth lining the esophagus. This can be traced upward to the limit of the plate. Figs. 56 and 57, together with the history, confirmed the diagnosis of hernia of the diaphragm.

Important diagnostic points demonstrated by the radiograms, Figs. 56 and 57: (1) The presence of a dark circumscribed shadow situated above the indistinct outline of diaphragm on the left side and bounded above by a curved dense band which does not maintain the dome shape typical of the normal diaphragmatic line, and limited mesially by the left border of the heart, which is displaced strongly to the right; (2) the presence of the shadows of the lower branches of the left hilus showing through rarefied area; (3) the location of the stomach and its great bubble by bismuth ingestion method.

included in a hernia, and a plate showing bismuth in the colon above the level of the bow-line in the chest would be conclusive evidence of a diaphragmatic rupture. So far as I have been

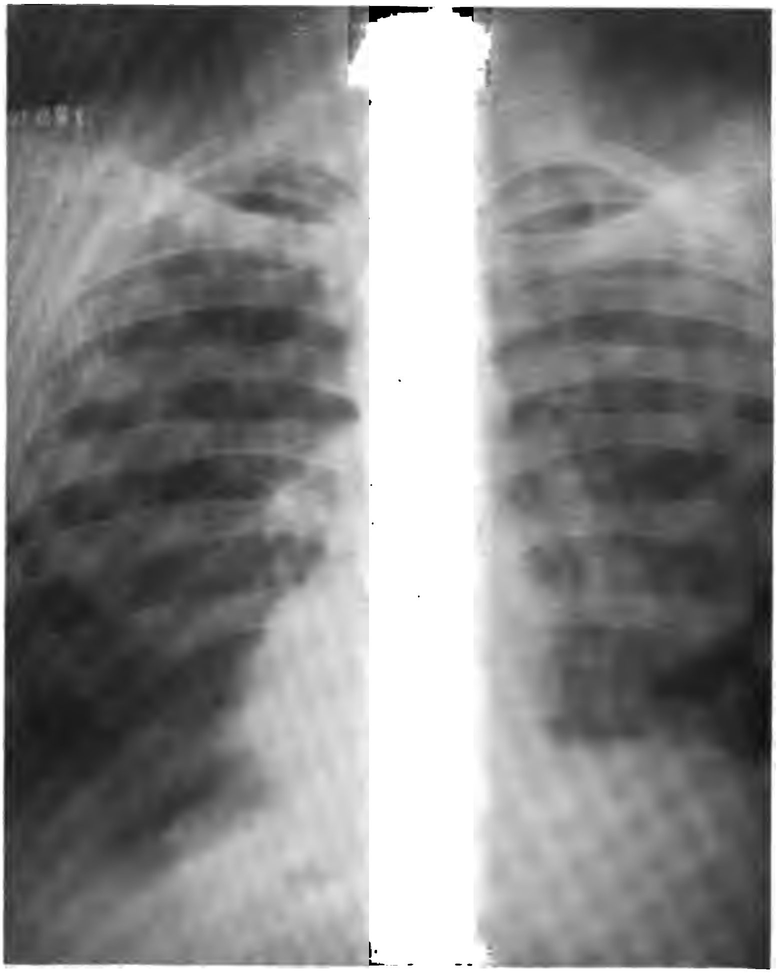


Fig. 58.

Two weeks after operation. (Compare with Fig. 56.) Patient's pose is the same as in Fig. 56. (1) Note the absence of the curved white line described in Fig. 56; (2) the dense white area just to the left and below the nose of the heart represents the operation scar; (3) the heart has returned almost to its normal position; (4) there is a marked difference in density in the two sides of the chest; the left is darker, indicating a pneumothorax and partial collapse of the pulmonary tissue incident to the operation upon the diaphragm.

able to learn, this point has not been emphasized in the literature, but *a priori* it would seem true.

Fluoroscopic examination is useful in studying the movements of the shadow-line. The excursion of the diaphragmatic line in

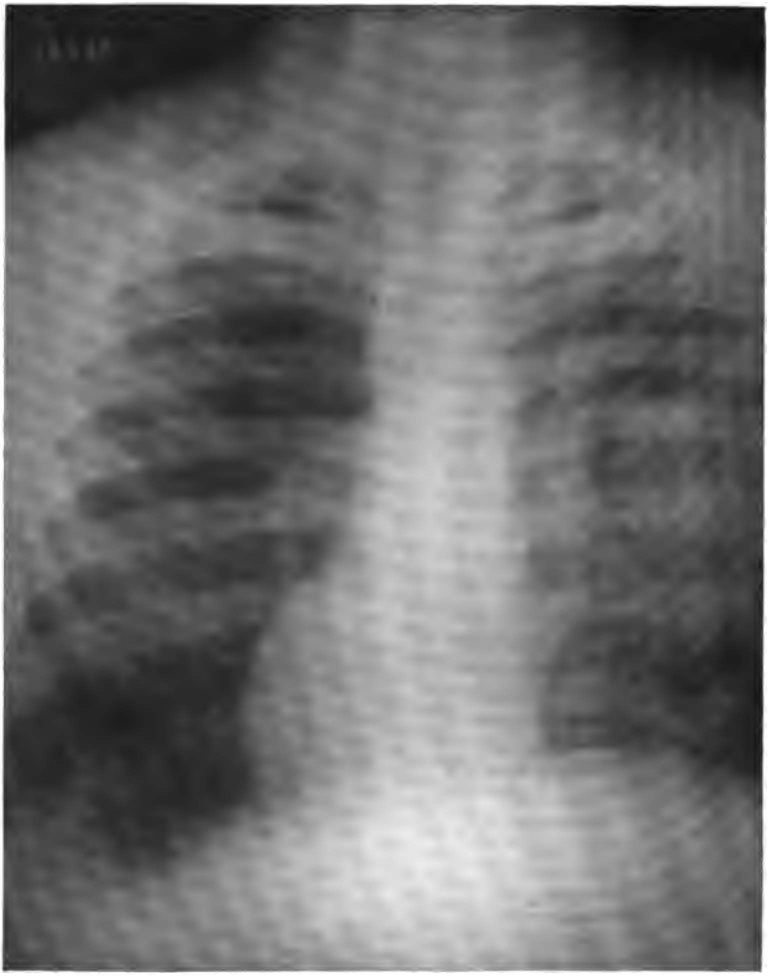


Fig. 59.

Three weeks after operation. (Compare with Figs. 56 and 58.) (1) The outline and position of the heart remain the same as in Fig. 58; (2) the shadow of the scar is greatly reduced in size; (3) the shadow of the pneumothorax has greatly decreased; (4) the pulmonary tissue has regained much of its normal appearance. Compare the right and left sides of the thorax.

elevation approaches in character the normal. On the other hand, congenital hypoplasia of the left lung is usually present with elevation of the diaphragm, and consequently the move-

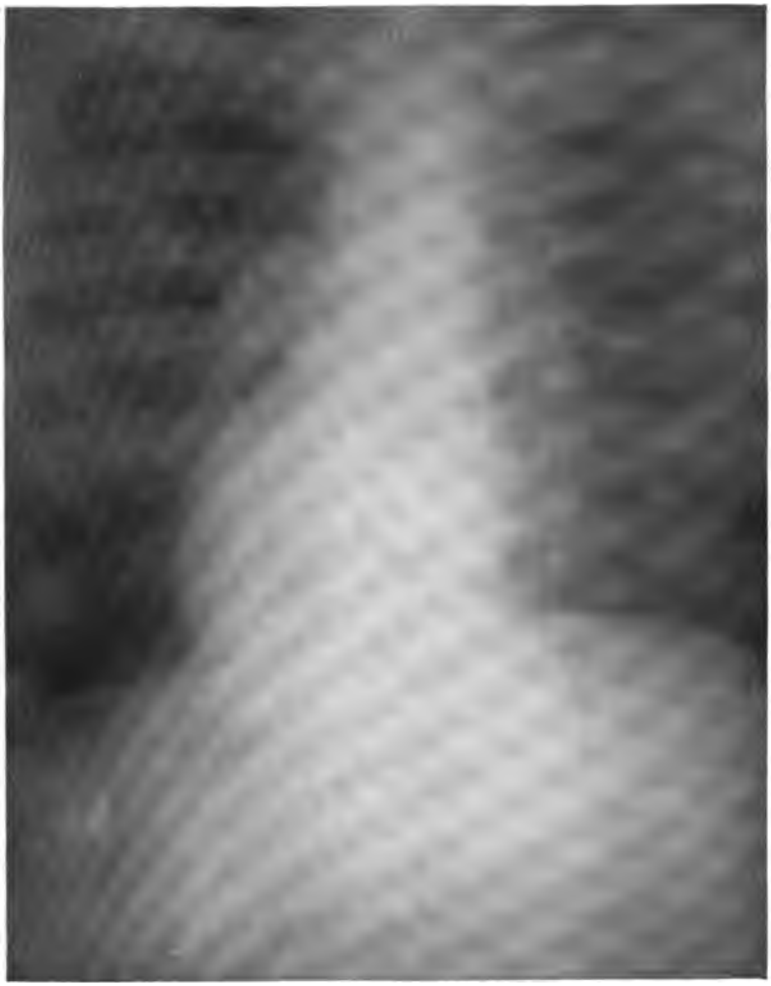


Fig. 60.

Six and one-half weeks after operation. (Compare with Figs. 56 and 58.) (1) The heart has returned to the normal position; (2) note the distinct change in the appearance of the scar of the diaphragm: it is much smaller; the outline of the diaphragm upon the left side is more nearly regular than in the preceding plates; (3) practically all trace of pneumothorax has disappeared and the lung tissue has resumed its normal appearance. Compare the left lung with the right.

ments of the diaphragmatic line may be far from normal. Indeed, a diaphragmatic shadow may not move with respiration in elevation and a stomach line may move in hernia. A "paradoxic expiratory displacement" has been noted in diaphragmatic hernia. During forced inspiration the right diaphragm descends normally, while the boundary line in the left chest ascends. During forced expiration the right diaphragm ascends while the boundary line on the left descends. Upon forced expiration by contraction of the abdominal muscles the shadow-line on the left is again forced high into the chest. The movements on the left occur a little later than those on the right. This phenomenon has not been described in unilateral elevation in which the movements of the shadow-line are likely to approach the normal in character, though they are less free in excursion. (See Becker's article, p. 186 *et seq.*)

The diagnosis then of diaphragmatic hernia from elevation of the diaphragm may, at times, be very difficult and may require all our technical resources. It is quite likely the *rudimentary elevation* is more common than at present suspected, and the condition should be more carefully looked for by clinicians.

The differential diagnosis of *pneumothorax* and diaphragmatic hernia is discussed in articles by LeConte and Ingalls. Particularly may there be difficulty when the pneumothorax is the result of injury. Dyspnea may be present, and severe pain be experienced. The note over the left chest may be tympanitic, and tinkling sounds be heard. The tympany, however, is likely to extend to the top of the lung, and the breath-sounds may be amphoric, vague, faint, or absent. In diaphragmatic hernia breath-sounds and vocal fremitus are not greatly diminished, and the metallic sounds are associated with peristalsis rather than respiration. The positive coin test is more constant in pneumothorax. Vomiting is likely to be less continuous. Bulging of the interspaces upon closure of the glottis may outline the lower limit of the lung. The radiogram will generally furnish conclusive evidence of an unbroken diaphragmatic line. Pneumothorax has protean characteristics, however, and diaphragmatic hernia should always be considered before a diagnosis of pneumothorax is made.

Pneumothorax from rupture of the stomach in congenital diaphragmatic hernia with no history of injury has been reported. Such a condition might possibly be suspected after very careful consideration, but it is difficult to see how a diagnosis could be established.

Hydropneumothorax should be less difficult of diagnosis, especially if fluid be present in a moderately large amount. If succussion be obtained, it must be determined that it is produced in the pleura and not in the stomach. A movable line of dulness with signs of pneumothorax and a horizontal fluid line in the radiogram would be conclusive. Leukocytosis and symptoms of pus infection in addition to the findings described above would point to *pyopneumothorax*. Exploratory puncture would be conclusive.

Temporary elevation of the diaphragm has been reported. It has been thought to be the result of an affection of the phrenic nerve. In time the diaphragmatic line resumes its normal position.

A large cavity in the lower lobe may give metallic sounds and dyspneic symptoms. The cavity may develop suddenly after the expectoration of large amounts of sputum. The radiogram would show evidence of lung involvement elsewhere, and it should be possible to recognize the diaphragmatic line.

The name *subdiaphragmatic pyopneumothorax* has been given to the condition in which a pus cavity beneath the diaphragm contains gas. The most common cause is perforating ulcer of the stomach or duodenum. The diaphragm may be elevated as high as the third rib. There may be tympanitic resonance over the area of the cavity. Metallic tinkle, succussion splash, and coin sound may be present. The chief difficulty would be in differentiation from pyopneumothorax. A history pointing to preëxistent abdominal disease and radiographic findings of elevation of the diaphragm should differentiate the condition.

In the case reported herewith, recurrent colic would have suggested *gall-bladder disease* or other abdominal lesion had a history of trauma not been obtained or had the findings on physical examination of the left thorax been less definite.

Pyloric stenosis has occurred from mechanic conditions in congenital diaphragmatic hernia, and the predominance of gastric symptoms has led to a suspicion of *ulcer*. *Esophageal stenosis* may be caused by acute hernia.

Four cases of diaphragmatic hernia have been operated on in the Mayo Clinic. Three of these were reported in 1909 by Beckman. The case seen since then was diagnosed by the writer from the history and clinical findings and independently from a study of the radiograms by Selby.

L. J. (a55100), male, aged twenty years. Consultation June 26, 1911. Patient had been caught, together with four other men, two of whom were killed, in a sand slide one year previously; he was instantly and forcibly doubled up with his head between his feet, was unconscious for five to ten minutes, but easily revived. The stomach was empty at the time of the accident. He experienced no pain for a half-hour after the injury. Then pain over the entire abdomen and chest became severe; shortness of breath was a prominent symptom, complaint gradually localizing to the upper abdomen and left side of chest and continuing together with some shortness of breath for two weeks. The patient remained in bed for five weeks. Pain across the lumbar region was also complained of, and the patient could not draw his legs up as he lay in bed for two weeks. Bladder and bowel control was good. He was able to walk in ten weeks. After this at times he complained of "sticking" pains across the abdomen and in the left side of the chest, and a sensation of the "stomach being lifted up under the chest." During the year which elapsed between the time of injury and the examination the patient had had attacks of severe epigastric pain lasting for an hour or two, with much bloating, sour eructation, and nausea, but no vomiting nor symptoms of intestinal obstruction. Pain often began in the right lower abdomen and later localized in the upper abdomen and left side of the chest. Soda gave some relief, but food did not. These attacks came at any time without relation to food and recurred every few weeks. There had been ten pounds loss of weight. Because of these attacks he consulted a physician. The family history and personal history were negative.

On physical examination a dull tympany was noted over the left side of the chest downward from the level of the sixth spine behind and anteriorly to the midaxillary line. Expansion did not seem to be markedly affected. Vocal fremitus was present over this area, though slightly diminished. The breath-sounds could be heard, but were quite distant. Tinkling sounds could also be heard, and these were close to the ear and seemed to occur with peristalsis. Anteriorly from the midaxillary line the percussion-note was quite dull, so that the left border of the heart could not be outlined. Heart dulness, however, extended three inches to the right of the midsternal line. Above the second rib in front and the spine of the scapula behind the percussion-note was hyperresonant and breath-sounds harsh. The right lung seemed normal.

The *x*-ray prints, together with their descriptions, by Selby, will explain the condition found. It is necessary only to point out that the diagnosis from the radiograms was made chiefly from—(1) The fact that the bow-line in the left chest did not conform in outline to the dome shape maintained in elevation of the diaphragm, and was irregular and indefinite, particularly at its outer portion; and (2) the fact that lung tissue could be seen through the gas bubble below this line, which is not observed in elevation.

Operation July 5, 1911: An oval-shaped opening in the left half of the diaphragm, near the crux, large enough to admit the hand easily, was found. The hernia contained stomach, large intestine, spleen, small intestine, and the tail of the pancreas. (The presence of spleen probably explains the dulness found anteriorly on percussion of the chest.) The lung was completely collapsed. The stomach was distended and its walls were hypertrophied, doubtless as the result of mechanic obstruction. Nearly all of the transverse colon and 12 feet of the jejunum were in the chest. The spleen was twice the normal size and most difficult to reduce. It was torn and required catgut sutures. Tremendous traction was exerted by the chest cavity, so that the stomach and spleen showed a marked tendency to be drawn back into it. The opening into the pleural cavity was sutured with heavy linen for three or four stitches, then interrupted sutures were placed. The suture line was 5 inches long. The posterior margin of the opening was difficult to catch, the anterior quite easy. Additional sutures were placed where there was evidence of air aspiration along the suture line.

It is impossible to determine what portion of the abdominal contents became a part of the hernia as the result of opening the abdomen. In view of the evidence of decided negative pressure in the chest upon the attempt at reduction of the hernia, it seems likely that the original hernia was increased in size by the additional pressure from below. The lung was found more nearly collapsed at operation than one would have expected from the extent of visible lung tissue in the radiograms.

Four days after operation the patient was quite comfortable and easily examined. The temperature was nearly normal. There were no signs of fluid. Over almost the entire left chest the percussion-note was exceedingly resonant, tympanitic, and so drum-like that it approached the quality of a musical tone. Vocal fremitus could be felt with difficulty and breath-sounds were distantly transmitted. The heart remained displaced. A pneumothorax was evidently present. One week later there was some change in the percussion-note. It continued, however, to be drum-like and very resonant. Breath-sounds could be heard a little closer to the ear save at the extreme left base. Cardiac dulness was almost normal in outline. The patient left the hospital on the thirteenth day. He was examined repeatedly up to the time of his discharge six and one-half weeks after operation. No complications developed. The lower portion of the lung slowly completed its expansion. An *x*-ray plate taken six and one-half weeks after operation is reproduced. This shows almost completed expansion of lung tissue. The return to the normal is remarkable when one considers that the lung had been partially collapsed for one year. The patient is at present enjoying excellent health.

On recapitulation then it is seen that a history of severe trauma, followed by upper abdominal and left thoracic pains, dyspnea, and vomiting, together with physical findings pointing to displacement of the stomach or intestine into the lower left chest and of the heart to the right, will ordinarily be sufficient for making a diagnosis of diaphragmatic hernia. If the history and findings be definite, this will be true whether the patient is seen immediately after injury or some time later. Röntgen-ray findings will then be mostly of corroborative value. When, however, the injury has been less severe and the symptoms and signs less definite, and again in most cases of congenital diaphragmatic hernia, radiographic and fluoroscopic examinations must be relied upon for a differentiation of the condition. In interpreting the plates—(1) A destruction of the definite dome shape characteristic of the normal diaphragmatic line; (2) the appearance of lung tissue through the gas-bubble in the left chest; and (3) the demonstration of bismuth in the colon abovet he level of the bowline of the chest, constitute the most important evidence in favor of hernia of the diaphragm. By fluoroscopic examination the "paradoxic respiratory phenomenon" may be demonstrated.

REFERENCES*

Becker: "Röntgenuntersuchungen bei Hernia und Eventratio diaphragmatica," "Fortschritte auf dem Gebiete der Röntgenstrahlen," 1911, vol. xvii, pp. 183–194.

Beckman: "Diaphragmatic Hernia," "Surg., Gyn., and Obst.," 1909, pp. 154–156.

Beltz: "Ein Beitrag zur Differentialdiagnose zwischen Hernia und Eventratio Diaphragmatica," "Münch. med. Woch.," 1910, vol. lxii, pp. 1006–1009.

Königer: "Zur Differentialdiagnose der Zwerchfellhernie und des einseitigen idiopathischen Zwerchfellhochstandes (infolge von Zwerchfell-Atrophie)," "Münch. med. Woch.," 1909, vol. lvi, pp. 282–285.

LeConte: "Rupture of the Lung without Costal Injury," "Annals of Surgery," 1908, vol. xlvii, pp. 383–389.

Ingalls: "The Diagnosis of Diaphragmatic Hernia," "Jour. Amer. Med. Assoc.," 1901, vol. xxxvi, pp. 1770–1774.

Sailer and Rhein: "Eventration of the Diaphragm, with a Report of a Case," "Amer. Jour. Med. Sci.," 1905, vol. cxxix, pp. 688–705.

Strüppler: "Über den physikalischen Befund und die neueren physikal. Hilfsmittel bei der Diagnose Zwerchfellhernie," "Deut. Arch. f. klin. Med.," 1901, vol. lxx, p. 1.

---

*The writer has collected a bibliography of 187 references. This will be furnished to any one particularly interested in a study of the condition.

THE REPAIR OF HERNIA FROM THE PERITONEAL SIDE OF THE ABDOMINAL WALL*

E. H. BECKMAN

It often becomes necessary to operate for abdominal conditions on patients who also have either femoral, inguinal, or umbilical hernias. For a number of years in such cases it has been the practice in the Mayo Clinic to repair these hernias from within the abdomen, provided they are not of enormous size. The operation was first used in repairing femoral hernias, and is similar to the Ochsner operation for this condition. The following is a description of the technic in a case of femoral hernia:

After the primary operation has been completed, the abdominal wall is retracted on the side of the hernia so that the femoral ring is exposed. A pair of artery forceps are then introduced through the hernial ring from within the abdomen to the bottom of the sac. The sac is grasped with these forceps and pulled back into the abdomen. Two or three mattress sutures of heavy linen or silk are then passed completely through the neck of the sac and tied. The remaining portion of the sac can then be either excised or stitched to the abdominal wall.

The most essential factor in the cure of a hernia is to obliterate the sac, and it will be seen that, following this operation, the sac is completely obliterated, and it is impossible for it to reinvert through the femoral ring.

In the cure of inguinal hernias by this method only those cases in which the sac is of small size are suitable, that is, the entire sac must necessarily be pulled back into the abdomen and the pillars of the internal ring sutured with mattress sutures of linen or silk, similar to the femoral hernia just described.

---

* Reprinted from "Annals of Surgery," April, 1912, p. 570.

In treating umbilical hernias by this method it has been our custom, on most occasions, to reinvert the sac of the hernia as described, although in some instances we have simply stitched up the ring with mattress sutures of linen, paying no attention to the sac, and have obtained equally good results.

THE OCCURRENCE OF RIGHT INGUINAL HERNIA FOLLOWING APPENDECTOMY*

DONALD C. BALFOUR

During only a comparatively recent period have surgeons considered the possibility of an added factor in the causation of right inguinal hernia.

We do not know whether the fact is generally recognized and accepted that the McBurney incision is occasionally followed by the appearance of an indirect hernia through the right inguinal ring. This point does not appear to be discussed in the more recent text-books on surgery, and we have not been able to find in the current literature more than two references to the subject: Hoguet[1] reports 8 cases in a series of 190 right inguinal hernias, and Pond[2] reports 1 case in a series which came under his observation.

The object of this communication is to present a brief review of the cases which were observed in the Mayo Clinic, and, if possible, determine the accuracy of the statement that the usual McBurney incision under certain conditions carries with it a risk of hernia developing at the right inguinal ring.

Of the 1889 operations performed in the Mayo Clinic within the past five years (from August 1, 1907, to August 1, 1912) for the radical cure of inguinal hernias, 314 were double, 795 right inguinal, and 466 left inguinal.

In a careful review of the histories in the series of right inguinal cases we found that in 17 the patients had been operated on previously for appendicitis through the ordinary McBurney incision, and that the first evidences of a hernia were noted by the patients at variable lengths of time after the appendectomy. A more detailed consideration of these 17 cases revealed that with the exception of a small direct hernia they were of the ordinary oblique type. Sixteen of the series were males, 1 female. Twelve of the 16 were between the ages of twenty and thirty years. In this series the periods between the operation and the appearance of the hernia were as follows:

---

*Read at ninth annual meeting, American Association of Railway Surgeons, Chicago, October 16, 17, 18, 1912. Reprinted from the "Railway Surg. Journal," November, 1912, vol. xix, pp. 117–119.

1 month	2
3 to 6 months	2
6 months to 1 year	3
1 to 2 years	2
2 to 3 years	1
3 to 4 years	0
4 to 5 years	2
5 to 6 years	2
6 to 7 years	3
Total	17

The above tabulation might suggest the question as to which of the cases are definitely dependent on the operation for appendicitis, basing the decision on the time that has elapsed since the operation. Bearing in mind that about 85 or 90 per cent. of hernias, both relapsing inguinal and the postoperative type, manifest themselves during the first twelve months following operation, we should not assume that cases developing later than one year could fairly be counted in this series.

Since the appendectomy had been done elsewhere in some of the cases, it was impossible to learn in all of them the details of the operative procedures, especially in regard to the use of drains and the length of time they were used. By adding the number in which accurate information was obtained to those cases in which the primary operation was performed in our clinic, we have 9 cases in which drainage was used for a variable length of time on account of the infection present. Several of these had also developed a postoperative hernia at the site of the appendectomy scar.

From facts brought out in going over the histories of these patients certain inferences may be drawn: It seems safe to assume that in a certain number of these cases the damage to the abdominal wall by the incision itself or by the pressure of whatever drainage was used was a contributing factor in the production of the hernia. It is also true that in the patients in whom the hernia developed a predisposition to hernia may have existed, owing to the presence of a latent small sac bulging through the transversalis at the internal ring. The explanation of this sequence may be found by referring briefly to the nerve-supply of the muscles in the region of the inguinal canal.

These muscles (the transversalis, internal and external oblique) derive their motor nerve-supply from the lumbar plexus through the ilio-hypogastric and ilio-inguinal nerves. These nerves traverse a course between the muscles of the abdominal wall, and, in the right lower quadrant of the abdomen, run more or less parallel with the ordinary gridiron incision. Both nerves are subject to various deviations from their usual course, and form inosculations one with the other, which are not constant. It is evident that the short McBurney incision for the removal of a chronic appendix cannot carry great risk of injury to the nerve-supply of the muscles of the inguinal canal, since the frequency of such operations would mean that more hernias would develop at the internal ring as a secondary result than have heretofore been reported. It is equally true, however, that when considerable traumatism to the abdominal wall has occurred at the time of operation by stretching and traction, or when drainage has been necessary, enough damage may have been done to the nerve-trunk to cause a deficiency of nerve-supply to the muscles and a consequent atrophy of greater or less degree.

It is not possible to decide whether or not the resulting hernia is of a true acquired type or merely the rendering evident of a preëxisting sac. Assuming that the great majority of indirect hernias are congenital in origin, it is reasonable to suppose that interference with the nerve-supply of the muscle has weakened the internal ring sufficiently to permit some of the abdominal contents to enter the latent sac.

The above data, *i. e.*, 17 hernias following the McBurney incision for removal of the appendix out of 795 operations for right inguinal hernias, are decidedly relative. Recognizing the fact that operations for appendicitis and hernias are exceedingly common, it follows that some of the cases may be mere coincidences. This possibility is well illustrated by 2 cases: In one, a left inguinal hernia occurred six months after the drainage of an abscessed appendix; a right inguinal hernia occurred five years later. In another case the patient had an appendiceal abscess drained at his home in 1905. In 1906 he was reoperated on in the Mayo Clinic for the closure of a fistula and the removal of the appendix. One and one-half years later he developed a large left inguinal hernia, and the following year a scrotal hernia on the right side.

It must also be assumed that hernias may have occurred following operations in our clinic of which we have no knowledge —the patients either have not returned for the repair of the hernia or they have been operated on elsewhere.

Admitting that some of the cases in the above series may have no interrelation between the operation for appendicitis and the development of the hernia, I believe that sufficient evidence may be drawn to warrant further investigation into the subject.

CONCLUSIONS.—(1) A McBurney incision which damages the nerve-trunks supplying the muscles at the internal ring may be followed by right inguinal hernia.

(2) This damage usually is dependent on the use of drainage and infection of the abdominal wall.

(3) The sequelæ in all probability occur in individuals who are already predisposed to hernia by the presence of a latent sac.

REFERENCES

1. Hoguet: "Annals of Surgery," November, 1911.
2. Pond: "Jour. Amer. Med. Assoc.," July 2, 1910.

UROGENITAL ORGANS

THE CLINICAL DIAGNOSIS OF CONGENITAL ANOMALIES IN THE KIDNEY AND URETER*

WILLIAM F. BRAASCH

In the literature of the past few years one may frequently find reports of one or two cases of congenital anomaly in the kidney and ureter. The existence of this condition was usually discovered at operation or at autopsy, and no extensive reference was made in regard to the exact clinical diagnosis. With the development of the cystoscope and the radiograph, and, more recently, through the discovery of the value of these instruments in their simultaneous employment, as in pyelography,[1] we now have at our command the means to make an accurate diagnosis in practically every case of renal or ureteral anomaly.

The frequent occurrence of congenital anomaly in the kidney and ureter is not generally appreciated. A review of the surgical and clinical records of the Mayo Clinic for the past five years shows that gross renal and ureteral anomalies were found in 36 patients. Of this number, 7 patients were operated on for diseased conditions in the abdomen other than those in the kidney, in whom the discovery of the renal anomaly was largely incidental to general abdominal exploration. Eighteen were operated on for various pathologic conditions complicating the anomaly. In the last three years we have been able to make the clinical diagnosis of congenital anomaly in 14 patients; of this number, 4 were not operated on, for various reasons. Postmortem records of the last 171 autopsies made at this clinic showed that congenital

---

* Reprinted from "Annals of Surgery," November, 1912, pp. 727–738.

anomaly of the kidney and ureter was noted in 7 cases, or over 4 per cent. of the total. This number includes only those gross anomalies occurring in the adult that might be regarded of surgical importance, and does not include minor anomalies, so frequently found in the urinary tract, such as supernumerary and aberrant renal blood-vessels, fetal lobulation, moderate degree of malposition, nor those rather frequent instances of partially deformed or moderately atrophic kidneys which may be due to either congenital or acquired etiologic factors.

The various anomalies, in the order of their frequency, were as follows: Fused or horseshoe kidney, 11; congenital, single, or asymmetric kidney, 6; atrophic kidney, 5; ectopic kidney, 3; duplication of renal pelvis and ureter, 8; division of ureter, 5.

The surgical records of the Mayo Clinic show 649 operations on the kidney and ureter during the past five years. Excluding the 4 cases diagnosed and not operated on, and the 7 cases found at autopsy, there remain 25 cases operated on, or a proportion of 1 congenital anomaly to 26.

The pathologic condition existing in the anomalous kidney or ureter usually calls our attention, clinically, to its existence. That such kidneys are peculiarly liable to disease has been noted by various observers. The frequency with which such anomaly is found in a surgical clinic as compared with postmortem records of a general hospital would, therefore, be at least partially explained by the fact that the complicating conditions usually require surgical treatment.

Fused Kidney

The fused kidney may assume any of a great variety of forms, and may be situated in various parts of the abdomen. The type of fused kidney more frequently found is the so-called horseshoe kidney. Although its usual position is in the median abdomen at about the level of the umbilicus, it often lies more to either side of the spine. Occasionally it will be found lying diagonally, with one pole extending down into the bony pelvis. If our attention be called to the existence of a fused kidney clinically, it is usually because of some pathologic process which causes tumor or localizes pain in the median abdomen. Unfortunately, the *subjective symptoms* caused by various pathologic conditions found in the horseshoe kidney might easily be confused with the symptoms caused by disease in the surrounding organs. When the complication involves one half of a symmetric lying horseshoe kidney, the pain may be more lateral than median, as proved to be the case in three of our series. When the kidney lies asymmetric, the median lying pole, which is usually the lower, is generally the one involved, with consequent distinctly median pain or tumor. Rovsing[2] has recently described 3 cases of symmetric lying horseshoe kidney without visible pathologic changes, which, because of their position, evidently caused pressure on adjacent nerve-trunks. He regarded the resulting pain, referred across the abdomen, appearing on exercise and relieved when recumbent, as pathognomonic. Our series includes one such case, but it was quite impossible to make the clinical diagnosis from the subjective symptoms. *Palpation* may determine a mass lying across the lower median abdomen, which is suggestive of a fused kidney, but certainly would not identify it as such. Furthermore, in a large or tense abdomen it may be quite impossible accurately to determine a small median tumor, such as may be caused by a median kidney. A retroperitoneal mass felt through the rectum may offer corroboratory data, particularly if the pulsation of adjacent large blood-vessels can be determined. This finding, however, can be obtained with various retroperitoneal conditions other than those of the kidney (Fig. 61).

The *radiographic shadow* of soft tissues in the abdomen is usually too inexact to permit of accurate interpretation. Occasionally the outline of a median mass in a thin subject may be suggestive of a horseshoe kidney. Should the radiogram show a shadow of an evident renal stone in the lower median abdomen, the possibility of a fused or ectopic kidney would be indicated. Meatoscopy may be of some corroboratory value. In 4 of the 5 cases thus examined the meati were found in their usual position in the trigone. In 1, the meatus of the ureter leading to the median lying pole was found in the median line of the trigone. Obstruction to the ureteral catheter at the level of a pelvic mass might be suggestive of some renal anomaly. However, more exact data are to be obtained through the combined use of the radiograph and the cystoscope, namely, through pyelography. The relative position of the pelvis is accurately determined, and any complicating dilatation or deformity of either pelvis and ureter can be clearly demonstrated. Within the past three years we were fortunate enough to secure 3 pyelographs of fused kidneys, all of which were complicated by a hydronephrosis in one of the poles (Fig. 62).

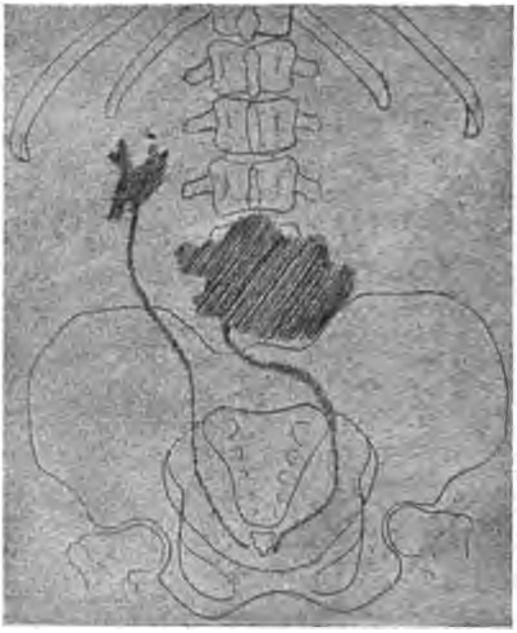


Fig. 61.—Horseshoe kidney. Case No. 10,215. Hydronephrosis, median and lower pelvis. Upper pelvis normal. Kidney resected.

On reviewing the 11 cases of fused kidney in our series, we find that 8 were of the so-called horseshoe type and 3 were so-called sigmoid kidneys, one with 3 separate pelves. The various conditions found complicating the anomaly were as follows: Hydronephrosis, 4; tumor (sarcoma?), 1; renal hematuria (essential), 1; abdominal pain, 1; discovered in operating for other abdominal conditions and evidently otherwise normal, 4. The sex was about equally divided, there being 5 males and 6 females. Six of the patients were below thirty years of age, and of these, 5 were operated on for some complication of the kidney itself.

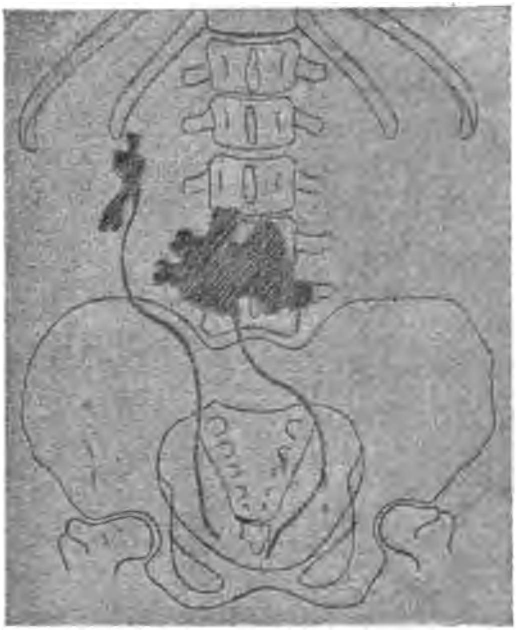


Fig. 62.—Fused kidney. Case No. 9508. Hydronephrosis median and lower pelvis. Upper pelvis normal. Kidney resected.

This is of considerable interest, and is in keeping with the fact that if complications (particularly certain forms of ureteral constriction) occur as the result of congenital anomaly, they will occur in the young adult, usually soon after their full development. The majority of anomalies occurring in patients over thirty years of age was discovered accidentally at the time of operation for some other abdominal lesion. Evidence of congenital anomaly in other organs was found in but one patient, a female, who was found to possess a bicornute uterus.

CONGENITAL SINGLE KIDNEY (Fig. 63)

The diagnosis of the congenital absence of one kidney can be made clinically only by means of the cystoscope, and thus the condition becomes a problem largely of cystoscopic technic.

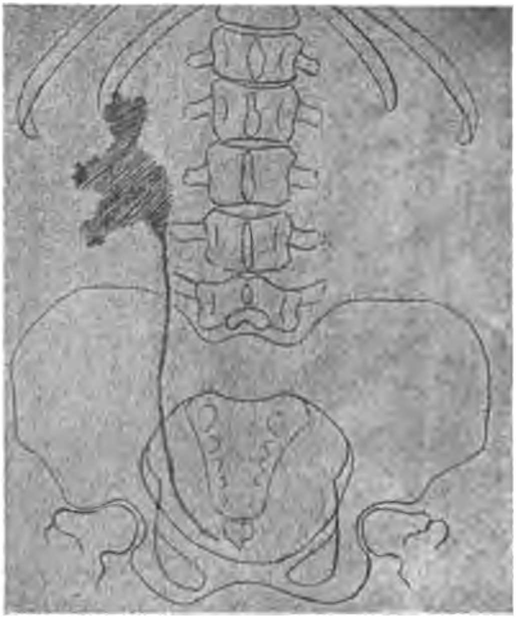


Fig. 63.—Congenital single kidney. Case No. 5244. Note large pelvic outline. Normal contour of calices.

Naturally, the inability to find a ureteral meatus in a markedly inflamed and contracted bladder does not necessarily indicate its congenital absence. In the hands of an experienced observer, however, the absence of any evidence of a meatus in a bladder which permits of thorough cystoscopic examination would be strong evidence of a single kidney. To further corroborate this, the segregator, if carefully employed, may be of value. The injection of indigo-carmin is often of aid in determining the existence of a meatus. Some difficulty may be encountered in differentiating clinically between acquired and congenital single kidney. When a kidney and ureter become functionless, *e. g.*, such as occurs with a so-called autonephrectomy, the site of the former meatus will frequently remain visible and show evidence of some inflammatory change. With the congenital single kidney the meatus is frequently situated in unusual positions, either in the median (one case) or extremely lateral base of the bladder (one case). Close examination of the meatus may reveal a hypertrophy of the muscular ring about it. The peristaltic contraction will be found exaggerated. The secretion may be found unusually frequent or with unusual volume.

Of considerable interest is the pyelograph of the single kidney. The injected pelvis of the hypertrophied congenital single kidney will usually appear considerably enlarged, but otherwise quite normal in outline.[2] The increase in the size of the pelvis will be commensurate with the increase in parenchyma. On the other hand, with an acquired single kidney the several pyelographs I have made do not show any increase in the size of the pelvis.

Although a portion of the other ureter has been reported to exist by various observers,[3] in none of the 3 cases cystoscoped and operated on, nor in the 2 cases reported in the autopsy records, was any evidence found of the other ureter.

A quantitative estimate of the functional capacity of the single kidney may be of some corroborative value. The phenolsulphonephthalein test is well adapted for this purpose. A very high percentage of the chemic substance secreted, such as usually occurs with two normal kidneys, might be indicative of the degree of compensatory hypertrophy.

Subjective symptoms are of little value.

Palpation.—To be able to palpate but one kidney and to determine an evident increase in its size are at best only suggestive of a single kidney. It must be remembered that one of two normal kidneys is occasionally found considerably enlarged without apparent reason. Frequently it is quite impossible to differentiate hypertrophy from a large normal kidney lying low and prominent in a thin abdomen. It may be difficult to differentiate between a small renal tumor and a hypertrophy. A tumor of the surrounding organs may closely simulate an enlarged kidney. If, however, on exploration in the abdomen the surgeon finds that one kidney is unusually large without apparent cause, the other kidney should invariably be searched for, and, if present, carefully examined for evidence of disease.

Of the 6 cases of congenital single kidney in our series, 4 were diagnosed clinically and demonstrated at operation. In 1 case the single kidney was tuberculous and in another the ureter was kinked so as to cause a moderate degree of mechanic obstruction. In but 1 patient was there any coexisting anomaly, namely, a bicornute uterus, a congenital absence of cervix, vagina, left tube, and ovary. The kidney was found markedly hypertrophied in every instance. This leads one to infer that where no marked hypertrophy is noted, absence of the other kidney may not necessarily indicate a congenital defect.

ATROPHIC KIDNEY

Atrophy of the kidney can be either congenital or acquired, and it may be quite impossible to differentiate the etiologic factors on gross examination. With a marked degree of atrophy of one kidney the other kidney is usually found hypertrophied. The discovery of hypertrophy in a kidney on abdominal exploration would necessitate examination of the other side. The clinical diagnosis of an atrophic kidney may be exceedingly difficult, and when made, is largely dependent on systematic data.

A moderate degree of atrophy could easily be overlooked in a cystoscopic examination. An evident diminution in amount of secretion on meatoscopy could easily be explained by reflex inhibition of secretion so frequently seen as the result of cystoscopic irritation. A qualitative estimate of the functional activity, as evidenced by the length of time required for the kidney to secrete a chemic substance previously injected subcutaneously, would be of little value so long as any normal kidney tissue is present. By means of a quantitative estimate we should be able to ascertain the functional capacity more accurately than by any other means. Unfortunately, however, with a diseased kidney on the other side the vagaries in functional estimate in the supposedly normal kidney are often so great that even a marked diminution in capacity does not necessarily indicate that the kidney in question is incapable of normal functional activity. Although a moderate degree of atrophy may be present without much evidence on cystoscopy, with marked atrophy; we have various data which should call our attention to its existence. Examination of the meatus will show an atrophy of the circular muscle usually seen about the normal meatus. The meatal contraction will be slight, the secretion will be small in amount, and seen but occasionally. The other meatus will usually show a corresponding compensatory increase.

Atrophy of the ureter is usually in keeping with the degree of renal atrophy. Such is often the case in conditions of reduced renal secretory tissue. Even a small ureteral catheter may be introduced with difficulty as a result of atrophic reduction in size of the ureteral lumen. The pelvis of the atrophic kidney, particularly in the congenital type, may be so rudimentary that its outline in the pyelograph is corroborative of the foregoing data.

The patient's general condition, blood-pressure, ophthalmoscopic data, as well as subjective symptoms, should call our attention to the existence of renal insufficiency in cases when the secretion from an atrophic kidney may appear normal. Atrophy of one kidney to such a degree that it would seem impossible to sustain life, and without apparent cause other than congenital, was found in 5 patients. In 2 cases the condition was found at autopsy, and in 1 case it was demonstrated clinically. The kidneys were described as infantile in size, and without other apparent evidence to cause their atrophy. The ureter was found small and atrophic in every case.

Ectopic Kidney (Fig. 64)

Anomaly in the position of the kidney may be acquired or congenital. A moderate deviation from the normal situation or a freely movable kidney is not necessarily considered a congenital anomaly. When, however, the kidney is found lying fixed in the bony pelvis or across the spine, and when its blood-vessels come from adjoining vessels, such as the iliacs, it must be regarded as a true congenital anomaly. Such a kidney is called an ectopic or pelvic kidney. Its clinical diagnosis is easily confused with various conditions in the surrounding organs. Subjective symptoms are usually referred to the lower abdomen and pelvis. On abdominal palpation the ectopic kidney may readily be mistaken for an appendiceal mass or a tumor of the adnexa.

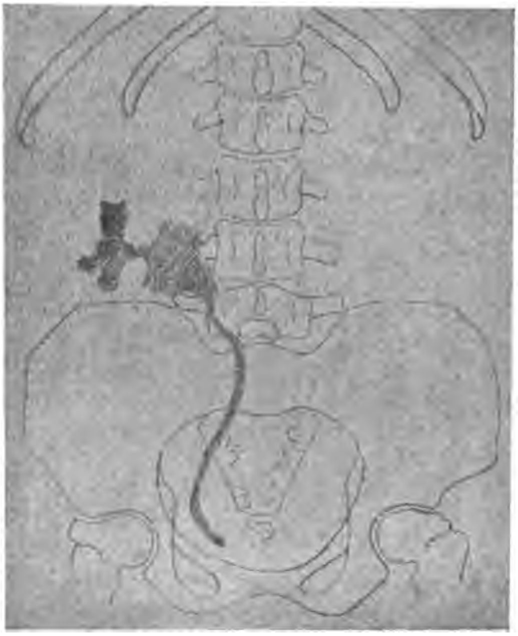


Fig. 64.—Ectopic kidney. Case No. 11,926. Note peculiar insertion of ureter (pelvis situated anteriorly). Duplication of pelvis.

On rectal examination it may, in some cases, be felt as a retroperitoneal mass, and when large blood-vessels are felt with it, the finding may be of value. However, the only accurate method of establishing the diagnosis clinically is by means of the cystoscope and the radiograph. On cystoscopy an anomalous position of the ureteral meatus may be present. The ureteral catheter can usually be introduced but a short distance. The position of a metal stilet or catheter, as shown by the radiogram, would localize the position of the kidney, providing the stilet would be introduced into the pelvis. More graphic and complete, however, is the pyelograph, which not alone localizes the position of the kidney, but also demonstrates any anatomic peculiarities in the renopelvic outline. It must be remembered that the relative position of the two pelves of an asymmetric fused kidney, one lying in a normal position and the other lying low in the median line, might simulate the relative position of the pelves of a normal lying and ectopic kidney. Since it is the existence of some pathologic condition which calls our attention to the anatomic anomaly, it is even more important that we demonstrate this complication clinically. The data obtained through the cystoscope and ureteral catheter alone will aid us materially in ascertaining the identity of the complication. The pyelograph will usually be found to be of greater value, however, to determine accurately the position and extent of any pelvic distention, whether mechanic or inflammatory, and to demonstrate any deformity resulting from inherent tumor. The most common complication associated with the ectopic kidney is hydronephrosis, evidently as a result of its anomalous position.

Ectopic kidney was found in 3 patients in our series. This number does not include those numerous instances where the kidney was found lying low in the abdomen, nor even those freely movable kidneys found in the bony pelvis. It includes only such as were fixed in the bony pelvis, and whose blood-supply came from the adjoining vessels. As various observers[4] have noted, malformations of the various genital organs frequently occur with such a kidney.

ANOMALIES OF THE URETER (Fig. 65)

Duplication of the Pelvis.—That the normal renal pelvis may assume any of a great variety of shapes is well known. The individual calices may be so large and so situated that they resemble separate pelves, particularly so when the calices do not unite until well beyond the hilum. When, however, there are two distinct pelves within the hilum, and each has its separate calices and ureter, the condition must be considered as an anomalous duplication of the pelvis and becomes of practical importance. Our series includes 8 cases of duplicated renal pelvis, 5 of which were operated on, 1 was found at postmortem, and 2 were demonstrated clinically but not operated on. In the 6 cases explored evidence of a division of the two halves of the kidney was externally visible, varying from a slight depression to a distinct area of

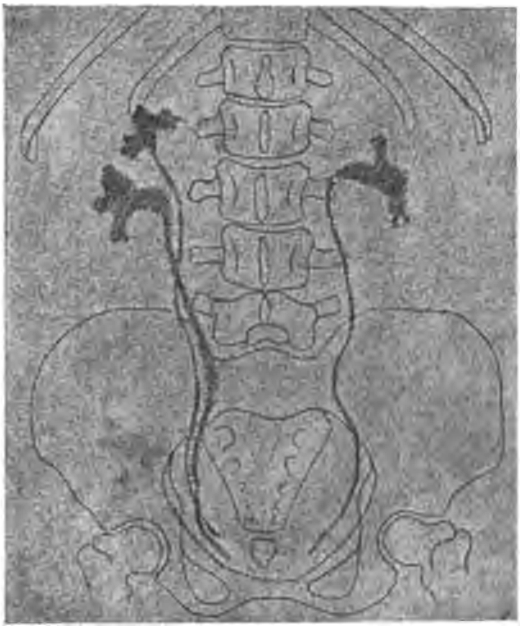


Fig. 65.—Case No. 10,962. Duplication of the pelvis of right kidney and ureters. Normal. Accidental discovery in routine clinical examination.

demarcation. The division is furthermore indicated in cases of true duplication by the fact that the individual poles of the kidney will have in the main a separate blood-supply. For practical purposes, therefore, the kidney might well be considered as made up of two distinct kidneys, which will permit of separation if necessary. Bisection of such a kidney was performed successfully in 3 instances by W. J. Mayo after the clinical diagnosis had been made. In 1 case duplication of the pelvis with separate ureters was found on both sides. In the right kidney the two pelves were united by a narrow calyx in common with both. This connection was suggested by injecting methylene-blue solution into one ureter and its return through the other. The separation of the pelves in all other cases was complete. The diagnosis of the pelvic duplication can be made accurately only by means of the cystoscope and radiograph combined. The finding of two separate meati on one side of the base of the bladder on cystoscopy does not necessarily indicate the existence of separate pelves, since the two ureters may unite above the bladder. Neither would two catheters introduced into separate ureters necessarily establish the existence of a duplicated pelvis, since a single pelvis may have two distinct ureters. The pyelograph offers the most accurate means of determining the relative position of the pelves and the amount of renal parenchyma separating them. Furthermore, it will determine the character and extent of any pelvic deformity which may result from some pathologic condition affecting that part of the kidney. The various pathologic conditions affecting the half of the kidney and necessitating operation were as follows: hydronephrosis resulting from anomalous blood-vessels constricting the ureter near the ureteropelvic juncture, 2; hydronephrosis resulting from stricture at the wall of the bladder, 2; hydronephrosis and stone, 1.

Duplication of Ureter (Fig. 66).—In 7 of the cases of duplicated pelvis in our series the two ureters were found separate along their entire course, and leading into separate meati in the bladder. In one case the two ureters were found lying in close apposition within a distinct sheath for a distance of about 6 or 8 cm. along their middle third, but without any evidence of anastomosis. The position of the two meati in the 4 cases cystoscoped and diagnosed was found to be variable. In 2 cases one meatus was found at about its normal position, while the other meatus was situated posteriorly and more median, about 3 cm. apart. In the other 2 cases the distance separating them was about 1 cm. The stilet or pyelograph will graphically demonstrate the usual crossing of the ureters at the brim of the pelvis. In 1 case we were able to demonstrate clinically complete duplication of the ureter on both sides, with partial duplication of the pelvis of the right kidney and complete duplication in the left.

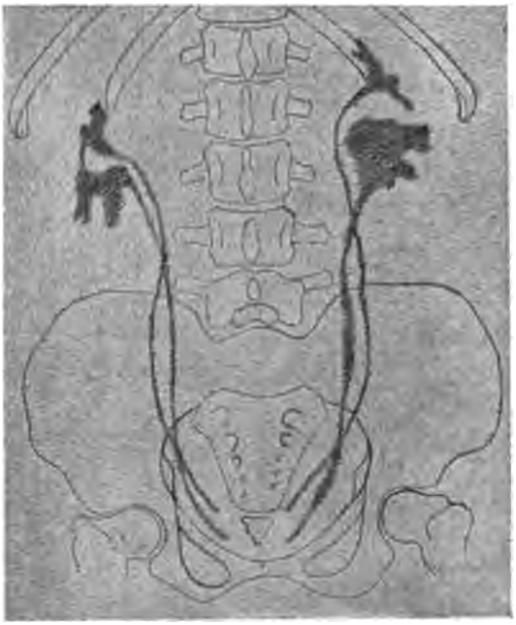


Fig. 66.—Case No. 13,529. Bilateral duplication of ureters and pelves. Duplication left kidney pelvis complete, with small hydronephrosis and stone of the lower pelvis. The two pelves of the right kidney united by common calyx.

Division or Partial Duplication of the Ureter.—The ureter may divide at any part of its course. The most frequent point of division is at the first portion of the ureter, where two more branches of the ureter leave the hilum and unite at a short distance below. Often, however, this will not be a true ureteral division, but will represent the absence of a true pelvis with the union of extended infundibula instead. Division of the ureter into two branches ending in adjoining meati is occasionally met with. This division may occur along any part of its course—more often in the lower portion. Union of the two ureters arising from normally situated kidneys and merging at about the brim of the pelvis and entering a single meatus on the right base of the bladder was found in one case of our series. This series includes 5 cases of division of the ureter; 1 case of double pelvis with 2 separate ureters joining a short distance below the hilum; 1 case of 3 ureters leaving a single large pelvis at various angles of the kidney, and

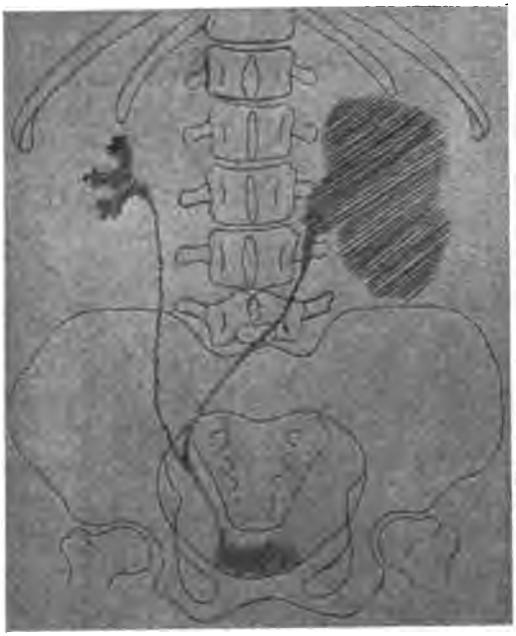


Fig. 67.—Case No. 11,425. Division of ureter at lower third. Left branch crosses spine and leads to a large hydronephrosis of the left kidney. Right kidney normal. Pyelograph obtained by using large catheter and inserting short distance into meatus.

uniting at a short distance below, which was found at autopsy; 2 cases of division of a single ureter at the brim of the pelvis entering separate meati on the same side; 1 case of union of the 2 ureters arising from separate kidneys at the brim of the pelvis, as described above, and which was diagnosed clinically by means of the radiogram following injection (Fig. 67).

The clinical diagnosis of duplication of the ureter can usually be made quite easily by means of inserting metallic coated catheters into the individual ureters, and then making a radiogram. This was done in 3 of our series of duplication. It will be found more difficult and often impossible, however, to so diagnose the divisions of the ureter. With division of a single ureter above the meatus it will be found necessary to inject fluids opaque to the *x*-ray in order to demonstrate the condition. This we were able to do in 2 instances. Furthermore, the radiogram following the injection will usually aid us in ascertaining the existence of any complicating lesion, such as stricture of the ureter and hydronephrosis.

The following complications were found in the cases of division of the ureter: (*a*) Hydronephrosis in a kidney with one ureter uniting with the ureter from the opposite kidney; (*b*) stone in ureter above point of lower division; (*c*) stricture in ureter at bladder.

REFERENCES

1. Braasch: "Annals of Surg.," November, 1910.
2. Rovsing: "Zeitschr. f. Urologie," 1911, vol. v, No. 8.
3. Anders: "Amer. Jour. Med. Sci.," March, 1910.
4. Monro: "Boston Med. and Surg. Jour.," March 31, 1910.

THE SURGERY OF THE SINGLE AND HORSESHOE KIDNEY*

CHARLES H. MAYO

The fact that developmental abnormalities of the genito-urinary system are the most frequent of any part of the body is not generally appreciated. Those involving irregularities of the circulation of the kidney are the most common of this group.

It is necessary for the surgeon of today to understand thoroughly these anomalies, and he is also much concerned over the functional activity of the kidney, not alone because of operations upon the organ itself, but also because of its great bearing upon all surgical operations.

A brief study of the early development of the genito-urinary system during the first few weeks of intra-uterine life simplifies our understanding of the common and curious derangements of the anatomy of this tract. Early in the life of the embryo the cloaca represents both the future rectum and the bladder. It gradually becomes divided by a vertical fold into two compartments—an anterior, with which the allantois and the primitive excretory ducts are connected, and a posterior, which becomes the lower end of the rectum. Entering the cloaca from the dorsal side are the two Wolffian ducts, which furnish the parent structures of the renal pelves and ureters. The Wolffian duct, while developed originally as a part of the pronephros,—the forward nephritic organ, which is exceedingly rudimentary in the human embryo,—is, throughout the greater part of its embryonic existence, the excretory duct of the Wolffian body or mesonephros. From these two primitive structures is developed most of the genitourinary system. The beginning of the permanent kidney—metanephros—appears in the human embryo of from 6 to 7 mm. in length as a tubular diverticulum, formed on the dorsal side of the Wolffian duct near the cloaca. This diverticulum is surrounded

---

* Read before the Southern Surg. and Gyn. Assoc., December, 1912. Reprinted rom "Annals of Surg.," April, 1913; "Trans. South. Surg. Assoc.," 1912.

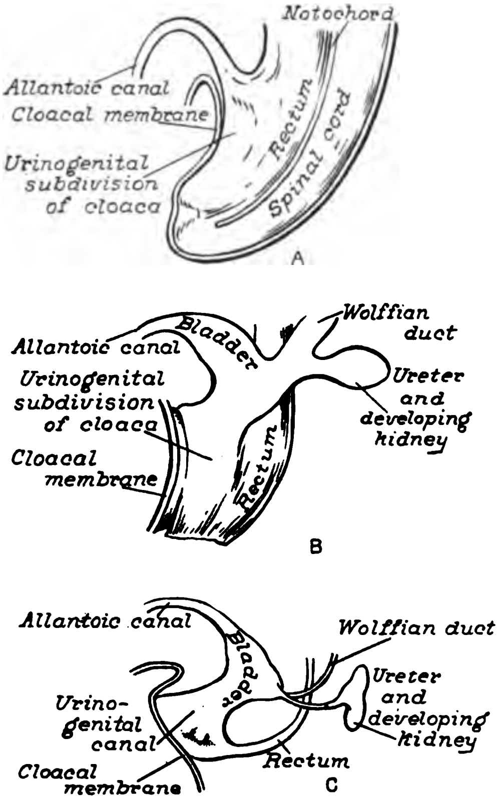


Fig. 68.—From model by Professor Keibel (Cunningham's "Anatomy").

from the first by a large group of cells (the renal blastema) which are of mesothelial origin, and which later form all the secreting portions of the kidney. The tubular portion of the diverticulum from the Wolffian duct becomes the ureter, while the distal extremity bifurcates into an upper and lower portion to form the pelvis, or collecting part of the kidney. As the bladder increases in size the single opening of the mesonephros and metanephros becomes a double one, consisting of the ejaculatory duct at the base of the bladder in the male and the ureter posterior to this (Figs. 68 and 69).

The kidney gradually ascends to the lower dorsal and upper lumbar region. As it ascends it passes and receives its blood-supply in succession from the numerous arteries previously developed from the aorta to nourish the mesonephros. As many as

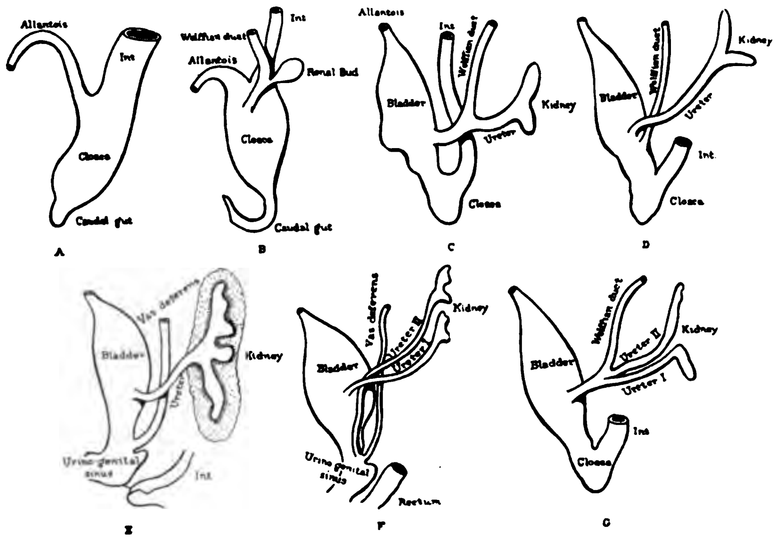


Fig. 69.—From Dr. George S. Huntington's paper on "The Genetic Interpretation and Surgical Significance of Some Variations of the Genito-urinary Tract."

five of the branches may be carrying blood to the kidney at once. As the kidney ascends and higher arteries become attached to it, the lower ones separate from it. When it reaches its final position, one of the arteries enlarges and becomes the permanent renal supply. This is usually the upper member of the lower or the lower member of the middle mesonephric group. Thus in anomalies of position the vessels may arise from the sacralis media, from the common iliac, the inferior mesenteric, or along the line of the aorta. If irregularly situated, they are usually increased in number. In the division of the kidney into upper and lower portions with separate pelves the division of the vessels permits of the removal of one-half of the organ without injury to the other half. In horseshoe kidney, however, Robinson[1] found 10 out of 60 cases reported, with but a single artery branching to each lateral mass, and 4 cases with a single trunk to the isthmus, with one branch to either lateral mass. In such cases the accidental destruction of the blood-supply of the entire kidney may easily occur during an operation on it.

There is nothing between the two renal mesenchymal structures during the early development of the kidneys but the forming aorta. Sometimes, indeed, they are in contact or even fused in front of or posterior to this vessel. This condition persisting, occasions some of the various anomalies under discussion. Rarely the secreting substance may become associated with but one collecting portion and ureter, and thus there may be but one kidney developed.

We may see the possible development of congenital cystic kidney resulting from a failure of certain portions of the secreting renal tissues to become connected with the collecting portion. Wilson[2] has called attention also to the probable development of the so-called hypernephroma as neoplastic growths from similarly unattached portions of the secreting portion of the kidney. The bifurcation of the end of the ureter may be so extreme that an upper and lower kidney may be seen on one side, with an upper cleft and a lower single ureter, or one completely cleft, varying according to the point of division of the metanephric diverticulum. The attachment of the secreting substance across the spine may drag one ureter across the midline. Two ureters to one kidney are not uncommon, and very rarely three ureters have been found, as in the case reported by Bransford Lewis.[3] In the other each calyx has a short ureter, all delivering through one ureter into the bladder, a form rarely seen in man. Küster[4] observed the right ureter formed of three branches, two being from the isthmus, while Gebhardt[5] reports one with five branches. We have seen two ureters to one kidney with variously located divisions, in five cases other than in those of the horseshoe type. The openings into the bladder may not be abnormal, depriving us of the aid of the cystoscope alone in making a diagnosis (Figs. 70, 71, 72, 73).

The ureter normally is 12 inches long. In a low placement of the kidney it may still be long and coiled or very short. Thompson's[6] case of pyonephrosis in a horseshoe kidney had a ureter 1½ inches in length.

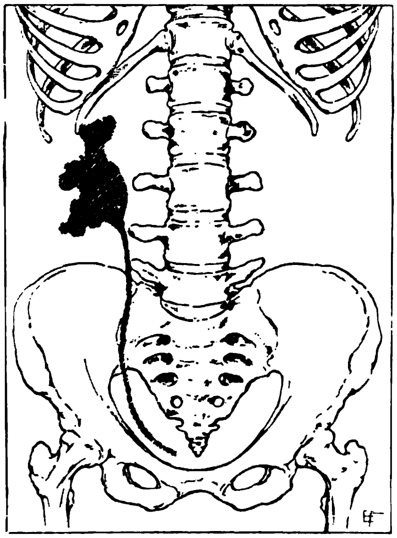


Fig. 70.—Case No. 5244. Congenital single kidney.

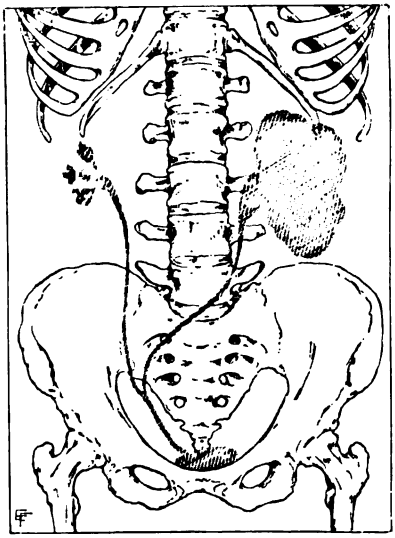


Fig. 71.—Case No. 11,425. Division of ureter at lower third. Left branch crosses spine and leads to a large hydronephrosis of the left kidney. Right kidney normal.

As to the relative frequency of this anomaly, it is difficult to say, since statistics vary so much. Those collected by Thompson[6] show 1 in 300 autopsies to those of others who place it as seldom as 1 in 1000. Our own autopsy records in a single year have shown as high as 4 per cent. of cases presenting gross anomalies of the kidney or ureter of surgical importance.

Of 36 cases of gross renal and ureteral anomalies observed during five years in our clinic, 7 were found incident to other abdominal operations. Among the total number were 12 of the horseshoe type and 6 of the congenital single or asymmetric type. During this five-year period 649 operations were made upon kidneys or ureters. Excluding those diagnosed and not operated on, and the cases found at autopsy, there was an average of one serious anomaly associated with the disease in every 26 cases, thus showing that such anomalies of kidney and ureter are often the cause of or are a contributing factor to disease of this structure (Figs. 74–82).

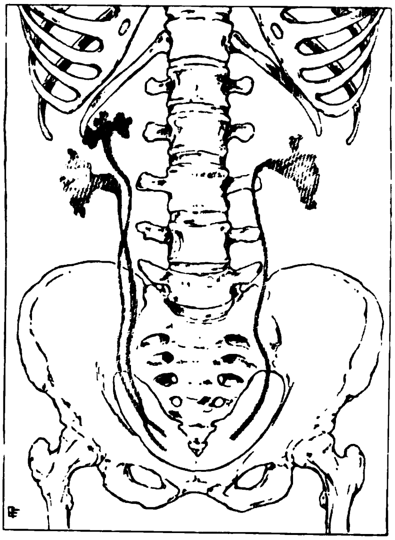


Fig. 72.—Case No. 10,962. Duplication of the pelvis of right kidney and ureters. Normal.

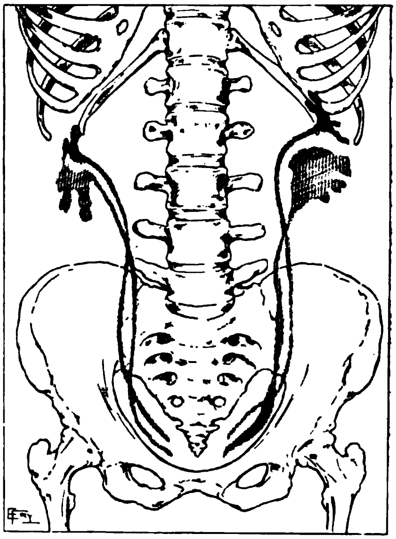


Fig. 73.—Case No. 13,529. Bilateral duplication of ureters and pelvis. Duplication left kidney pelvis complete, with small hydronephrosis of the lower pelvis. The two pelves of the right kidney united by common calyx.

Robinson's collected statistics show that in the horseshoe form 90 per cent. are fused at the lower poles, and in the others it was reversed, the convex surface being upward. If the positions of the kidney are not symmetric, they are of the "L" shaped or irregularly fused form, the lower kidney being drawn to the midline. At the point of union there may be only connective tissue (in 15 per cent. of the cases); usually, however, it consists of true renal tissue, and varies from a small area to the full width and thickness of the kidney. Robinson found 90 per cent. of cases fused in front of the great vessels.

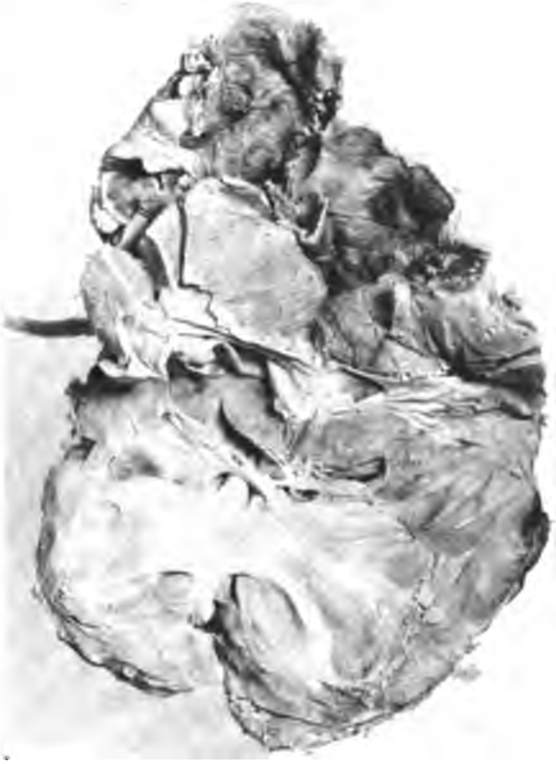


Fig. 74.—Exterior of horseshoe kidney, showing large hydronephrosis caused by valvular constriction of ureter at ureter-pelvic juncture.

Among the irregular forms are the sigmoidal—upper and lower pole fused—and the unilateral gross kidney.

Several classifications of horseshoe kidney exist. The oldest grouping by Neufville and Freund[7] admitted form as a criterion, the attachment being at the lower or upper poles. That of Förster[8] was based on the degree of fusion, regardless of the point of attachment. The classification of Heuer[9] was based on situation, and included unilateral and "L" shaped kidneys. That of Carlier and Gerard[10] is based on form and situation. They state that a horseshoe kidney is a congenital malformation consisting in a connection, more or less close, of two similar poles of the kidneys in front of the spine, showing more or less clearly the form of a horseshoe, with equal or unequal branches. They divided them into two classes—symmetric and asymmetric.

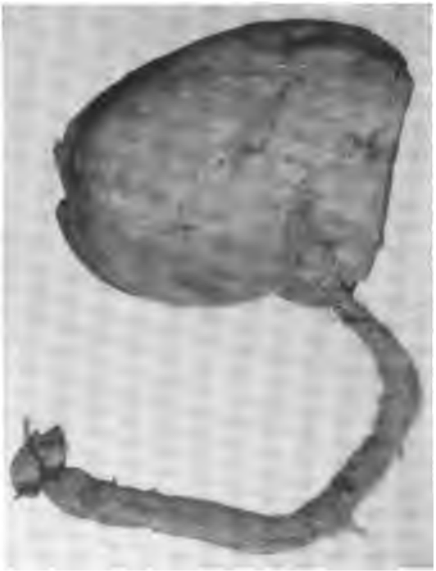


Fig. 75.—Half of double kidney and ureter. Removed at operation for stricture of ureter.

The most common disease affecting horseshoe kidney is hydronephrosis, which later may develop pyonephrosis. Hydronephrosis occurs in moderately young individuals, while pyonephrosis and lithiasis, which also occasionally may be found in horseshoe kidney, are usually seen in middle age or later. All three of these conditions may be present in one side of such a kidney.

Tuberculosis is rarely seen, but when present, is diagnosed by the usual symptoms of hematuria, bladder disturbance, and the finding of tubercle bacilli in the urine. It is located by cystoscopy and the separation of the urine from the two sides. König[11] and Gibbon[12] each report sarcoma of one half of the kidney in children, both cases recovering from a transperitoneal removal of the growth. Cystic tumors of such kidneys which have necessitated the removal of one half in one and puncture of cysts in another have been reported by Bockenheimer.[13] With reference to sex, more horseshoe kidneys are found in women than in men, and more single kidneys in men than in women.

For a long time the observations made upon horseshoe kidney agreed that the condition could not be discovered save at operation or autopsy, except in those cases where the abnormal kidney attained a pathologic alteration. Since surgical interventions were rare, patients suffering from grave troubles, due to the presence of horseshoe kidney, died without the cause of their symptoms being ascertained. It is very probable that some of these symptoms do not produce sufficient disability to cause the patient to consult a physician, especially when the connecting link between the kidneys is connective tissue. Heavy renal tissue so placed undoubtedly gives symptoms if we can rightly interpret them.

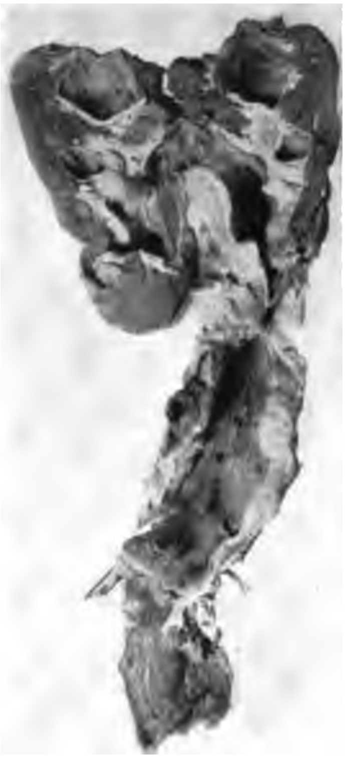


Fig. 76 —Section of horseshoe kidney half showing (1) large hydro-ureter caused by stone in bladder; (2) pyonephrosis.

Rovsing's[14] recently published cases of horseshoe kidney with operative verification are very suggestive. In 3 cases the same symptomatology was noted, the predominant symptom being pain experienced in the abdomen and lumbar region and beneath the epigastrium. These pains generally radiate downward and usually manifest themselves while the patient is standing upright, being then almost continuous. They are mitigated greatly by rest, and disappear completely after prolonged rest in bed. These patients suffer severely from continuous jarring, and the suffering is increased by muscular effort, such as lifting. Throbbing and a sense of pressure in the abdomen may occur, and upon bending backward their discomfort is greatly increased. From their situation such kidneys are more liable to injury, compression of the abdominal vessels may occur, and a case of thrombosis of the iliac and femoral veins, causing edema of the legs and ascites, as reported by Neufville.[15]

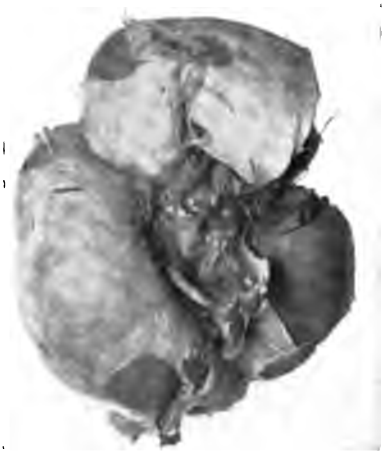


Fig. 77.—Half of horseshoe kidney. Removed at operation for hydronephrosis.

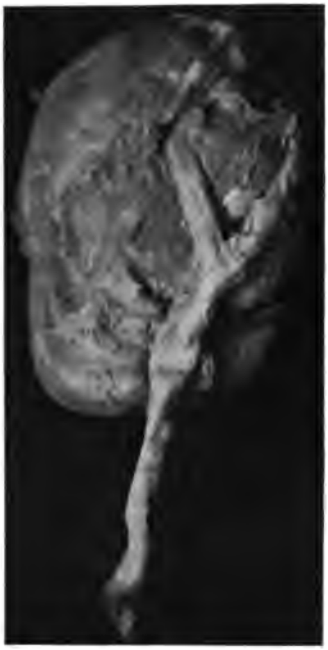


Fig. 78.—Note division of ureter into three parts at site where the renal pelvis should have been. (Autopsy specimen.)

In the diagnosis of horseshoe kidney the associated anomalies of the genital system are to be considered, as they are developed together. Such conditions are frequently noted with congenital cryptorchidism, hypospadias, atresia of the anus, double or bicornute uterus, absence of vagina, etc. Such cases have been reported by Tillmanns,[16] Gerster,[17] and others.

In spite of the fact that there are sufficient data upon this subject to permit of a diagnosis, it will not, as a rule, be made before operation, except in the minority of cases, until the subject is kept more in mind by the diagnostician. Most of the cases reported are accidental findings in the course of operations on the kidney or other abdominal organs, or are contained in post-mortem reports. In a number of instances horseshoe, irregular, or gross single kidneys have been removed from the body before a diagnosis has been made. We have at our disposal, then, the

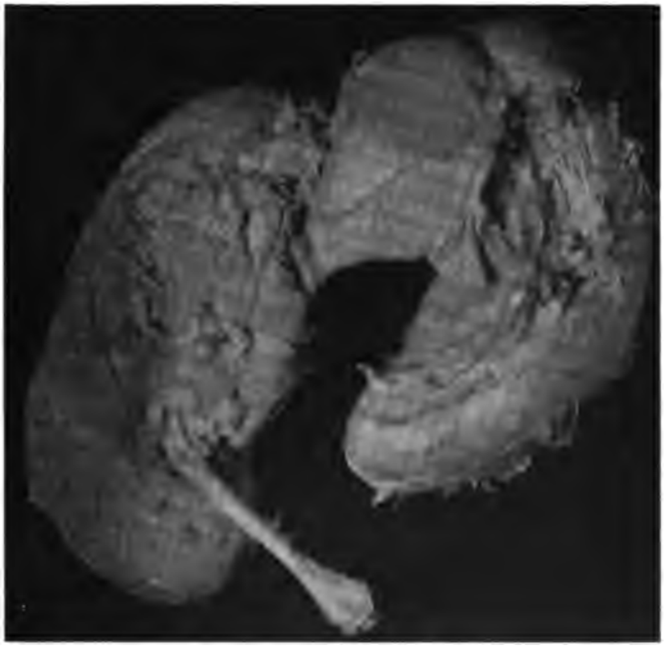


Fig. 79.—Exterior of horseshoe kidney. Note lobulation. Kidney could be easily divided at either interlobular depression.

physical examination, and, as Braasch[18] points out, in addition to the cystoscope and radiogram, the great assistance obtained by pyelography with colloidal silver injections. The latter are more accurate than the opaque ureteral catheter, especially in establishing the diagnosis of multiple ureters and pelves. In horseshoe kidney and irregular varieties of double kidney of a congenital type, in the congenital single kidney (more rare than horseshoe kidney), and in the single kidney with atrophy or destruction of the other through disease, we have conditions which tax the diagnostic ability of the surgeon to the utmost. The lesson we must learn in every case in which we are not positive

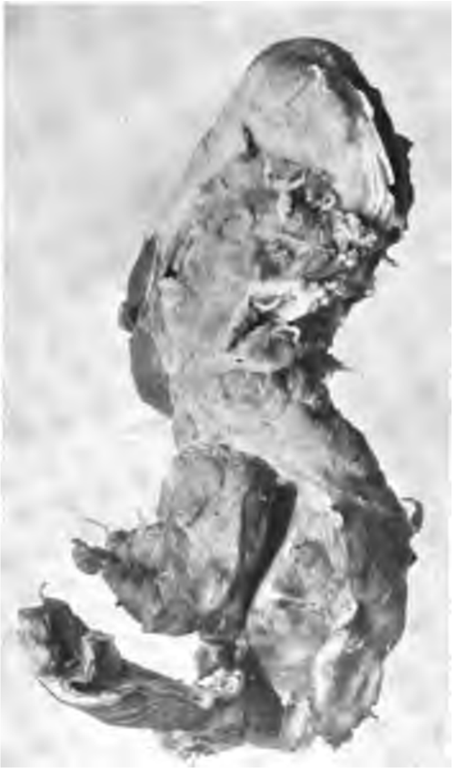


Fig. 83.—Exterior of one-half of horseshoe kidney with ureter removed at operation.

of the condition, then, is always to explore the other kidney, usually through a separate incision, before removal of a tumor of the kidney or the removal of a diseased kidney, and in abdominal surgery in which tumors of unknown type and origin are discovered, regardless of location, the kidneys should be palpated before removal of the tumor.

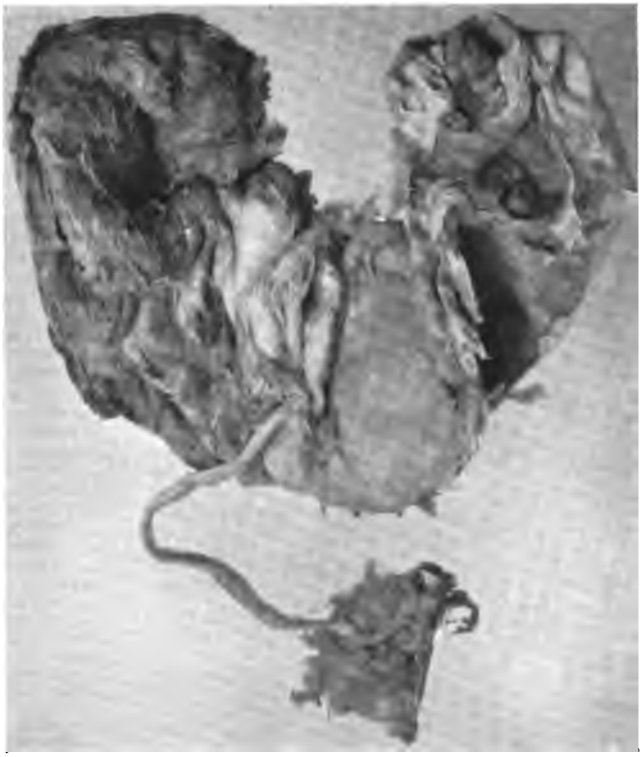


Fig. 81.—Exterior of horseshoe kidney with but one ureter. No distinct narrowing between the two halves. (Autopsy specimen.)

Operation.—In some instances the incision will be a transperitoneal one. The lateral incision described by W. J. Mayo[19] will suffice in most cases. It is as follows:

"Beginning at a point 2 to 2½ inches lateral to the dorsal spines, near the outer margin of the erector spinæ muscle, a longitudinal incision is made, 2 or 3 inches in length, through the skin, superficial fascia, and posterior layer of the lumbodorsal fascia (vertebral aponeurosis), which covers the erector spinæ muscle. The incision lies behind the twelfth rib from the angle, if present, nearly to the head, and reaches downward to a point one-half inch below the angle. From this point the incision passes obliquely downward and forward along the anterior margin of the quadratus lumborum muscle, to a point an inch above the crest of the ilium, and there, turning, runs forward parallel to the iliac crest as far as necessary.

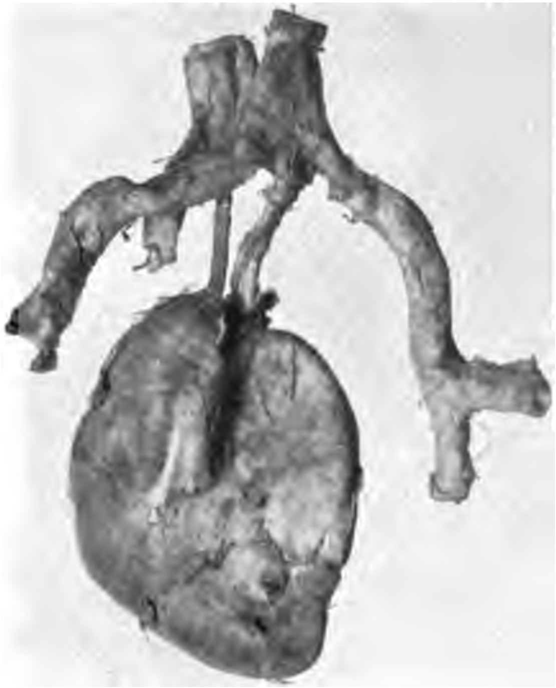


Fig. 82.—Pelvic kidney, showing blood-supply arising at juncture of iliacs and entering upper pole of kidney (autopsy specimen).

"The posterior superior lumbar triangle (Kelly) just beneath the twelfth rib is then exposed by cutting an opening through the external and internal oblique, transversalis, and latissimus dorsi muscles, exposing the transversalis fascia in its lumbar portion. This fascia is then opened freely, exposing the perirenal fat. The ilio-inguinal and iliohypogastric nerves are identified and retracted out of harm's way, and the lower part of the incision completed. The twelfth rib is then cleared in its posterior portion upward and backward nearly to the articulation of the rib with the transverse process of the twelfth dorsal vertebra, and the pleura pushed upward. By retracting the erector spinæ muscle, on the one hand, and the costal margin, on the other, a wide exposure is accomplished at the point of previous inaccessibility. As a rule, the kidney can readily be drawn through the incision to the surface with but little traction. The incision is easily closed, and there is little or no danger of hernia."

As these cases will often be discovered during operation on the kidney, the possibility of horseshoe kidney must be considered when it is unusually difficult to deliver the lower pole. This occurred in my last case, one of pyonephrosis of half of the horseshoe kidney. The renal tissue, nearly the full size of the normal kidney, passed in front of the large vessels. After examination of the blood-supply, which is so frequently abnormal in such cases, this tissue was divided and sutured with catgut. In a case that was not pathologic other than the abnormality, Rovsing relieved the pain and general symptoms by division of the isthmus.

REFERENCES

1. Robinson: "Lancet-Clinic," August 7, 1909, pp. 141–148.
2. Wilson: "Old Dom. Jour. Med. and Surg.," April, 1910, pp. 237–252.
3. Lewis: "Med. Rec.," October 6, 1906, pp. 521–524.
4. Küster: "Deut. Chir.," vol. lii, p. 241.
5. Gebhardt: Rayer, vol. iii, p. 771.
6. Thompson: "Annals of Surg.," September, 1911, pp. 354–359.
7. Neufville and Freund: Quoted by Carlier and Gerard, "Rev. d. Chir.," July and August, 1912.
8. Förster: "Missbildungen des Menschen."
9. Heuer: "Ueber Hufusennieren," Diss., Leipzig, 1902.
10. Carlier and Gerard: "Rev. d. Chir.," July and August, 1912.
11. König: "Deut. Zeitschr. f. Chir.," vol. xl, p. 92.
12. Gibbon: "Rev. d. Chir.," 1909, p. 1265.
13. Bockenheimer: "Berl. klin. Woch.," vol. xlviii, September 4, 1911.
14. Rovsing: "Zeitschr. f. Urol.," 1911, vol. v, No. 8, 1911, pp. 586–601.
15. Neufville: *Loc. cit.*
16. Tillmanns: "Deut. Zeitschr. f. Chir.," Lief 62, A, 706.
17. Gerster: "Mt. Sinai Hosp. Rep.," 1905, vol. iv, pp. 165–177.
18. Braasch: "Jour. Amer. Med. Assoc.," December 16, 1911, pp. 1986, 1987.
19. Mayo: "Annals of Surg.," January, 1912, pp. 63–65.

THE RESULTS OF THE EARLY DIAGNOSIS OF URINARY TUBERCULOSIS*

WILLIAM F. BRAASCH

Notwithstanding the fact that much has been said and written within the past few years concerning tuberculosis of the kidney, many of the patients suffering with this disease are not referred for operation until the process is well advanced. Up to January 1, 1912, the records of the Mayo Clinic show that 212 patients were operated on for renal tuberculosis. Of this number, 159 (71 per cent.) had symptoms suggestive of renal tuberculosis which had extended over a period of more than one year; 37 (17 per cent.) over five years, and 13 (6 per cent.) over ten years. Only 61 patients (29 per cent.) had symptoms of less than one year's duration, and but 21 (10 per cent.) less than six months. During the past ten years we have examined 71 patients, who, because of complications or because both kidneys were diseased, were regarded as inoperable. Of this unfortunate number 61 (86 per cent.) had symptoms of renal tuberculosis extending over a period of one year; 34 (48 per cent.) over five years; and but 10 (14 per cent.) less than one year.

The question naturally arises, How is it possible that the tuberculous process should be allowed to go on so long without surgical intervention? The more important reasons appear to be as follows: (1) The true nature of the disease still too frequently remains unrecognized by the general practitioner; (2) it is not generally known that surgery is the best means to cure tuberculosis of the urogenital tract; (3) there exists a wide-spread belief that renal tuberculosis can frequently be cured by means other than surgery, particularly through the use of tuberculin.

---

*Reprinted from "Interstate Medical Journal," 1912, vol. xix, No. 10, pp. 863-869.

That the presence of renal tuberculosis is usually recognized through the irritability which it causes in the bladder is a fact frequently disregarded. For the best interests of the patient it would be well to regard every case of *diurnal* irritability of the bladder, persisting over a period of several months and accompanied by more or less pyuria, as due to renal tuberculosis until it can be proved otherwise. However, we undoubtedly meet with a large number of cases of irritability of the bladder from causes other than renal tuberculosis. Excluding those patients having symptoms of prostatic and urethral obstruction, we have examined, during the past year, 327 patients complaining of irritability of the bladder, and a diagnosis of renal tuberculosis was made in but 39 of them. The remaining cases may be grouped in two divisions: (1) Those with little or no actual inflammation of the bladder; (2) those with cystitis. The first group is by far the larger, including 201 patients in whom cystoscopic examination showed little or no inflammation. This group of cases is composed largely of women of the fourth or fifth decad, and with many the vesical symptoms seem to be a form of neurosis. The majority of these cases can be recognized by the fact that the patients have little or no nocturnal frequency, and also by an examination of their urine, which usually shows little or no pus. The symptoms, however, while extending over a period of months or years, will not be persistent. The other group of non-tuberculous cases was composed of the following forms of cystitis: (1) Non-specific cystitis; (2) pyelitis and cystitis; (3) cystitis accompanying vesical neoplasm and stone; (4) cystitis with infections in the prostatic urethra. This second group might readily be confused with renal tuberculosis, since considerable pus and persistent irritability of the bladder may be common to both. These cases will require further differentiation. While vesical symptoms usually first call our attention to the existence of a renal tuberculosis, occasionally the initial symptom will be a pain, referred to the affected kidney, which may become very severe. In exceptional cases a sudden hematuria will be the first indication of the infection. However, these symptoms are early accompanied by irritability of the bladder and various other evidences of renal tuberculosis. Strange to say, the most common diagnosis and the condition for which many patients had been treated was that of Bright's disease. The diagnosis was frequently made because albumin was found in the urine, no further urinary examinations being made. Gonorrhea was also often assigned as the cause of the vesical symptoms, in spite of the fact that Neisserian infection is found in comparatively few cases as a cause of cystitis.

Given, therefore, a patient with persistent irritability of the bladder, what steps are to be taken to determine whether or not the symptoms are caused by renal tuberculosis? A careful examination of the urine. If no pus be found, even through microscopic examination, tuberculosis can be excluded in most cases. With pus present in considerable quantities, the early diagnosis of tuberculosis becomes largely a problem of demonstrating the presence of the tubercle bacillus. It is peculiarly true that sputum is examined for tubercle bacillus as a matter of routine by hundreds of clinicians, but the urine seldom is examined, although the technic is practically the same. The tubercle bacillus can be found in the urine of practically every case of early renal tuberculosis if looked for repeatedly. If, however, with a case of persistent diurnal irritability of the bladder and pyuria the tubercle bacillus cannot be found microscopically in a catheterized specimen, and we have reason to suspect its presence, a guinea-pig should be inoculated with the sedimental urine. Particularly in early infection is the guinea-pig test practically infallible, and it is unfortunate that because of the expense, technical difficulties, and length of time involved, the method is not more generally available.

When, however, the guinea-pig test is not available, and the microscopic examination is necessarily uncertain, we have other evidence which is corroboratory of the condition—namely, cystoscopic and physical examination. The presence of nodular enlargement of the epididymis or prostate is of particular value in physical examination, and it should be looked for in every case of irritability of the bladder in the male. In fact, when such enlargement is found in a young adult, without recent venereal infection or nocturnal frequency, the diagnosis of renal tuberculosis can be made safely. Thickening of the ureter, renal tumor, temperature, loss of weight, radiographic data, etc., usually appear later in the progress of the disease. Without going into the details of the cystoscopic picture of the tuberculous bladder, suffice to say that while it is not necessarily pathognomonic, particularly in the early stages, it can, nevertheless, usually be recognized by an experienced observer. The various tuberculin reactions, including cutaneous and Calmette's tests, are not of great practical value, since, while a positive reaction may be indicative of tuberculosis, it is of no value in localizing the process.

Localization of the disease is the next and a very important step to complete our diagnosis. This is entirely a question of cystoscopic technic, and it is frequently a most difficult one even in the hands of an experienced observer. By means of the cystoscope we are able to determine (1) the degree and character of infection in the bladder; (2) whether infection is secondary to the kidney or to the epididymis and prostate; (3) which kidney is involved and the degree of involvement; (4) to a certain extent the functional capacity of the remaining kidney; (5) whether both kidneys are involved.

Granted, therefore, that negligence accounts to some extent for the fact that the true nature of the irritability of the bladder, in a large percentage of cases of long standing, is not recognized, there is still unfortunately an increasing proportion in which the nature of the disease has been recognized, but treated by nonsurgical measures. The various methods by which renal tuberculosis has been claimed to be cured are as follows: Spontaneous, climatic, heliotherapy, and tuberculin. Within the last few years we have records of a number of patients who have been treated by various means, and particularly with tuberculin over a period of several months or years, before presenting themselves for operation, and in none of whom was any marked improvement noted. While it may be true that incipient renal tuberculosis may occasionally recover spontaneously, it has been our experience that such a case is so exceptional that it should not be relied upon. Our files, up to January 1, 1912, record 283 cases diagnosed as renal tuberculosis; 212 patients have been operated on, leaving 71 who were not operated on. Of those not operated on, we were able to trace 48. Ten patients were reported alive; 2 between five and ten years, 4 more than three years, and 4 more than one year. Of this number, we have found but 3 in whom the tubercle bacillus has disappeared from the urine and in whom the vesical symptoms have ceased. Two of these cases are of less then five years' duration and the third is of eight years' duration. It is of interest to note that the 3 patients were young adults, less than twenty years of age, in whom the progress of the disease is usually more rapid than in patients above forty. There are left then 38 patients who are known to have died, or a non-operative mortality of 80 per cent. These figures probably do not represent the exact truth in leaving the non-operative cure of 20 per cent., since, in the first place, but few patients will survive after ten years, and, secondly, the majority of those not traced are probably dead. Of those regarded as inoperable, our records show 26 patients in whom both kidneys were infected. Twenty of these gave a distinct history of infection in the second kidney from two to ten years after the first kidney became diseased. Although we advised 12 of the latter to try tuberculin, all with one exception have since died.

The patients who were operated on included 14 in whom the symptoms had practically ceased for intervals of several years—in 4 cases as long as ten years and in 1 case twenty years. Cystoscopic examination in these cases demonstrated absence of secretion from one kidney and obliteration of its ureter. This condition is the result of a process which has been called autonephrectomy. It is undoubtedly far more common than is generally believed, and accounts for a large number of so-called spontaneous cures. At operation, the kidney is found to be necrotic and filled with caseous or a semi-solid purulent substance, which had persisted for many years as a menacing source of infection. While a good many sporadic cases of so-called recovery have been reported by various observers, but few of them have been observed long enough—at least ten years—to determine whether or not the recovery is permanent. If spontaneous recovery were as frequent as is claimed by some observers, we should, at least occasionally, find evidence of healed tuberculous kidneys. But few, if any, of such specimens have been reported. Israel[1] states that tuberculin is of no value whatever in the treatment of renal tuberculosis, and should not be used even in the very earliest stages of the infection. Blum[2] recently reported 26 cases not operated on, of whom 22 died in from one to three years after observation; many of these, however, were bilateral.

Wildbolz,[3] in the last German Congress of Urology, reported a careful study of 316 cases of renal tuberculosis treated in Switzerland by various Swiss physicians, by methods other than surgical. His summary is of exceptional value and quite conclusive, since Switzerland is supposed to have climatic conditions favorable for the treatment of tuberculosis, and contains many sanatoria for that purpose. All his patients had careful bacteriologic, and many of them had cystoscopic, examinations made. Postmortem records were available in many. Of this number, he reported that 70 per cent. had died—60 per cent. in less than five years. Most of them died of complications resulting from infection in the urinary tract. Only 10 per cent. were alive more than five years after the beginning of the disease; in only 5 per cent. had all symptoms ceased over five years; and but one case was well in every respect. These observations agree with those made at the Mayo Clinic, and prove quite conclusively that permanent recovery from renal tuberculosis without surgical removal of the diseased kidney is exceptional and not to be relied upon.

It is generally recognized that the results of surgical treatment, while not satisfactory in every case, are followed by cure in the majority. In a recent paper[4] the writer gave the results obtained in 203 cases operated upon in the Mayo Clinic for renal tuberculosis. The immediate operative mortality (2.9 per cent.) was so low as to be practically disregarded. Those patients (18) operated on during the current year and those that could not be traced (43) were excluded from the summary of first operative results, leaving but 142 patients, or 70 per cent. of the total number to be considered. Of this number, 116 (82 per cent.) were reported alive more than a year after operation, 98 (69 per cent.) being well or greatly improved, and 18 (13 per cent.) reported little or no improvement in vesical symptoms. A closer analysis of those reported with symptoms unimproved shows that 83 per cent. had a history of infection of more than two years' duration. Of those patients who had symptoms of less than one year's duration, 81 per cent. were well or markedly improved. Furthermore, the convalescence and relief of symptoms of those with recent infections were much earlier than those of long-standing infection. Worthy of note is the fact that 22 per cent. of those reported dead had symptoms of one year or less. It is hardly conceivable, however, that the operation would materially influence the patient's resisting power. The prognosis of patients operated on in less than a year after the onset of symptoms is, as a rule, much better than those operated on later.

It has been claimed that the high death-rate during the first year after operation (in our series 61 per cent. of all reported dead) goes to prove that the operation was the cause of death. While it is possible that the operation may in some way lower the already weak resisting powers, it seems more logical to suppose that the patients would have succumbed to the disease even if not operated on. While it is true that complications outside the urinary tract do not necessarily contraindicate operation, nevertheless when present the prognosis is rendered less favorable. Evidence of previous complication was found in 19 per cent., and active lesions in 10 per cent. of the patients operated on. Of those reported dead, 41 per cent., had some evidence of extra-urinary complication at operation. Renal tuberculosis, secondary to pulmonary tuberculosis, was found in but 4 of the cases observed, and all were inoperable. Pulmonary tuberculosis, secondary to renal tuberculosis, was found in 26 patients, most of whom had a renal infection of several years' standing, except 2 who had miliary tuberculosis. Twelve of the patients were operated on, 6 of whom were reported alive. Of the latter, 3 had but slight involvement and 2 were doubtful. The remaining 14 cases were terminal complications of long-standing renal infection. Tuberculosis of the bones and joints as a complication seemed to have a more favorable prognosis. Spondylitis appears to be exceptional, however, since the 3 patients with spondylitis were reported dead within a year following operation. Marked involvement of the prostatic gland renders the prognosis less favorable. Of the 24 males with such involvement who were operated on, 11 (46 per cent.) were reported dead. Stricture of the urethra was found in 12 cases; in 9 it was found and considered inoperable. In the 3 patients operated on, 2 were reported dead within a year after operation. The stricture occurred usually in cases of long-standing infection and recent bilateral complication or in cases of rapid and virulent infection.

The following complications might be considered as the principal contraindications to operation: (1) Advanced pulmonary infection; (2) *multiple* accompanying lesions, such as in the joints and bones, prostatic abscess with perineal fistula; (3) peritonitis; (4) marked bilateral involvement; (5) clinical evidence of renal insufficiency. The prognosis of a patient whose kidney has been removed for tuberculosis will depend largely upon his resisting power to future tuberculous infection in other parts of his system. It would be unreasonable to suppose that nephrectomy would increase this resisting power other than to remove an active source of infection. Whereas outdoor life, rest, etc., are of little value in the cure of an active renal tuberculosis, it is of considerable value in the prophylaxis of postoperative tuberculous complications. The question has arisen, How soon after the detection of the disease should the kidney be removed? It has been argued that enough time should be given for the normal kidney gradually to hypertrophy. However, experience has shown that a normal kidney can readily perform the function of two when the second kidney is suddenly destroyed. Rather than risk spreading the infection, it would seem that the kidney should be removed as soon as the tuberculous lesion can be ascertained.

CONCLUSIONS

(1) The existence of renal tuberculosis should be suspected in every case of persistent diurnal irritability of the bladder; (2) no such case should be treated without a thorough examination of the urine for the tubercle bacillus; (3) early nephrectomy offers the best chance for cure; (4) the longer the patient's bladder is infected, the slower is its recovery in spite of nephrectomy; (5) with most cases of bilateral infection the second kidney becomes infected some time after the first kidney is diseased, and the infection is evidently transmitted from it; (6) non-operative cure, either spontaneous or through the use of tuberculin, climatotherapy, etc., is exceptional and at best symptomatic; (7) the risk of severe vesical infection and of transmission of the disease to other parts of the body through delay is too great to warrant the small chance for cure by non-operative means.

BIBLIOGRAPHY

1. Israel: "Zeitschr. f. Urologie," erstes Beiheft, 1912, pp. 25–28.
2. Blum: "Zeitschr. f. Urologie," 1909, vol. iii, pp. 238–268.
3. Wildbolz: "Zeitschr. f. Urologie," erstes Beiheft, 1912, pp. 29–74.
4. Braasch: "Jour. Amer. Med. Assoc.," February 10, 1912, pp. 397–401.

CLINICAL DATA ON MALIGNANT RENAL TUMORS*

WILLIAM F. BRAASCH

The surgical records of St. Mary's Hospital, Mayo Clinic, show that 83 malignant tumors of the kidney were operated on up to July 1, 1912. The tumors are classified according to their histologic structures as hypernephroma (mesothelioma), sarcoma, carcinoma, and embryoma. Clinical differentiation, according to the above histologic classification, usually cannot be made prior to exploration. From a clinical point of view, therefore, the various forms of tumor will be considered together.

As has been noted repeatedly by various observers, the cardinal symptoms of malignant renal tumor are hemorrhagic urine, tumor, and pain. Given a clinical picture of a palpable tumor in the region of the kidney, hemorrhagic urine, persistent pain referred to the region of the tumor, and the general symptoms of malignancy, the diagnosis of malignant renal tumor will usually be found correct. These complete data, however, were found present in but 32 of the 83 cases under consideration. Two of the 3 symptoms were present in 37 cases, and but 1 symptom in 14 cases. It is evident, therefore, that the clinical diagnosis must more often be made with but 1 or 2 of the cardinal symptoms.

SYMPTOMS

Hematuria.—Probably the most important symptom in malignant renal tumors is hematuria. It was given as a symptom observed by the patient in 53, or 64 per cent., of the cases; as a primary symptom in 39, or 36 per cent.; and as the only symptom in 10, or 12 per cent., of the cases. In 41, or 77 per cent., hematuria was noted more than a year before the patients presented themselves for operation. Gross blood in the urine was found at the time of examination in 33, or 40 per cent., of the cases. As a symptom observed by the patient only, hematuria may be of doubtful value. An occasional hematuria may be disregarded or forgotten by the less intelligent individual, by the female, who may believe it to be of menstrual origin. Again, patients frequently give a history of slight hematuria which may originate from some passing condition in the bladder or urethra. Thus in 50 cases of tumor in the surrounding organs which did not involve the kidney but resembled tumor on palpation a history of possible hematuria was obtained in 4, or 8 per cent., of the cases. A positive history of repeated hematuria was obtainable in but 41, or 50 per cent., of the cases. Gross blood in the urine at the time of examination is of the greatest value. Of what value is the finding of microscopic blood? In 21 cases of renal tumor blood was found only on microscopic examination. In the last 50 cases of abdominal tumor which, on palpation, simulated renal tumor, but which, on exploration, were found not to involve the kidney, 6 cases showed microscopic blood in the urine. The possible causes for the existence of a few blood-cells in the urine are so many that their discovery microscopically is really of little practical diagnostic value.

---

*Read before the Canadian Med. Assoc., Edmonton, August 14, 1912. Reprinted from "Jour. Amer. Med. Assoc.," January 25, 1913, pp. 274–278.

Tumor.—In 65 patients, or 78 per cent., a tumor mass could be felt on clinical examination; its existence was known to 28 patients, or 34 per cent. of the total; it was the first evidence of disease in 12 patients, or 15 per cent.; 37 patients were unaware of its existence, although the majority of them had had more or less medical care previously; and it was given as the only symptom by 5 patients, or 6 per cent. The tumor was described as freely movable in 5 patients, or 6 per cent.; as slightly movable in 45 patients, or 54 per cent., and fixed in 15 patients, or 18 per cent. In 12 of the latter the tumor was found inoperable on exploration. Palpation of tumors in the zone of the kidney is frequently found of very uncertain diagnostic value, even when aided by percussion and bowel inflation, and presents many possibilities for error. The following data in palpation of the kidney may be of practical value:

1. Tumors of the surrounding organs so frequently simulate renal tumor in position, form, and consistency that it is quite impossible to differentiate them by means of palpation alone.

2. Renal tumor, particularly when involving the lower pole, may extend irregularly toward the median abdomen or down into the pelvis, so as to simulate tumor of the various extrarenal organs.

3. Renal tumor may be very uncertain on palpation—(*a*) When the kidney lies high; (*b*) when the tumor involves the upper pole; and (*c*) when it occurs in a fat abdomen. It is frequently astonishing how large the tumor is found to be at operation when, on palpation, an enlargement could not be determined or was considered questionable.

4. Kidneys otherwise normal are occasionally found so large that they simulate tumor on palpation. This hypertrophy may be found to occur without apparent reason, or as the result of diminished function in the other kidney.

5. Low-lying large kidneys in thin patients may simulate moderate tumor enlargement.

Pain.—When it accompanies renal tumor, pain is caused either through tumor pressure on the surrounding nerve-trunks or by means of increased intrarenal tension resulting from interference with urinary drainage. When caused by tumor pressure, the pain may be referred to various parts of the upper abdomen and back, and consequently will often be misleading. Not infrequently will the pain radiation simulate that of gall-bladder disease; again, it may readily be mistaken for that of lumbago or muscular rheumatism. Abdominal pain of varying degree was complained of by 68, or 82 per cent., of the patients. It was given as a primary symptom by 27, or 32 per cent., and as the only symptom by 14, or 17 per cent. The pain was referred—(*a*) To the affected kidney region in 50 cases, or 74 per cent.; (*b*) to both kidneys in 4 cases, or 6 per cent.; (*c*) across the back in 11 cases, or 17 per cent., and (*d*) it was diffuse and of no localizing value in 8, or 12 per cent. Of the cases of pain referred to the affected kidney, several occurred with hematuria only, and in all probability were the results of blood-clots obstructing the ureter. Epigastric distress with more or less nausea was noted by 8, or 12 per cent., of the patients, and in 4 instances it was given as the predominant and only symptom.

Evidence Afforded by Urinalysis.—Other than blood in the urine (which has been discussed previously), pus may be found to a varying degree. Gross pus was found in 5, or 6 per cent., of the cases, and microscopic pus in 15, or 18 per cent. Occasionally the pyuria becomes so marked that the condition may readily be confused with a pyonephrosis. Usually only a small amount of pus is found in the catheterized specimen, and it may be the result either of secondary infection due to interference with the drainage of urine by the tumor or to tumor necrosis.

Circulatory Disturbance.—Evidence of circulatory disturbance is commonly found with the so-called hypernephroma or mesothelioma. In fact, this condition is observed so often as to indicate that toxins absorbed from the tumor may have a vasomotor dilating effect. Dilatation of the superficial blood-vessels is apparent in the face, the bladder, the scrotum, and in hemorrhoids. The dilated superficial veins of the face not infrequently cause a flushed, congested appearance, which is almost pathognomonic. Dilated veins in the scrotum or varicocele occur more commonly with hypernephroma than is generally recognized. A history of a varicocele of recent onset in a patient of forty years or over renders an unidentified hematuria or tumor very suggestive of hypernephroma. Varicocele should always be searched for when renal tumor is suspected. Two of the patients at the Mayo Clinic had previously been operated on elsewhere for varicocele. In the last 30 males the condition was found in 9, 4 on the right side and 5 on the left. In 3 instances a recent hydrocele was noted which might have been coincidental. Hemorrhoids of recent appearance were noted in 5 of the last 30 patients.

Dilated blood-vessels in the bladder were noted on cystoscopic examination in 4 of the last 50 patients. Cardiac dilatation is a rather common late symptom, and was found in 10 of the 21 cases clinically considered inoperable. While dilatation of blood-vessels in the scrotum, bladder, and rectum occasionally occurs with various abdominal tumors, and may then be explained by mechanic pressure, the peculiar frequency with which they are found with renal tumors, together with the venous dilatation in the upper extremities and the common cardiac insufficiency, must be explained by causes other than mechanic.

Differential Diagnosis

The principal problems in differential diagnosis are identification of hematuria and upper abdominal tumor. The conditions which may most easily be confused with renal tumor are—(1) "Essential" and nephritic hematuria; (2) retroperitoneal tumor; (3) bilateral cystic kidney, and (4) closed pyonephrosis. Hematuria prolonged over a period of several weeks or months and occurring at long intervals is suggestive of "essential" or nephritic hematuria; when it continues but a day or two and reappears at short and irregular intervals, it suggests renal tumor. With an otherwise symptomless hematuria, the question frequently arises whether or not surgical exploration is indicated. It has been our rule not to operate on cases of symptomless renal hematuria unless the loss of blood was so great as to interfere with the patient's duties. When, however, repeated severe hemorrhages occur in a patient of forty years or over, with loss in weight and strength, even though neither tumor nor pain exists, exploration may be justified. Illustrative of this point is a case which recently came under our observation. The patient, a man aged fifty, complained of hematuria persisting for three months, with loss of weight of 15 pounds. Tumor and pain were absent. Cystoscopic examination demonstrated the source of bleeding to be the right kidney, but gave no other data. Exploration revealed a kidney normal in size and form, but appearing moderately pale. On section, numerous small areas of pale tissue were visible. Microscopic frozen sections demonstrated tissue from these areas to be hypernephroma, and the kidney was then removed. Although interstitial hypernephroma is extremely rare, renal tumor revealing itself clinically only by hematuria occurs often enough to warrant exploration in doubtful cases. Acute pain with essential or nephritic hematuria is exceptional, although it must be remembered that blood-clots occasionally cause acute colic.

Hematuria with bilateral cystic kidney may be confusing when the renal enlargement can be felt only on one side. Chronicity of symptoms and clinical evidence of renal insufficiency and bilateral tumor may call our attention to the cystic nature of the tumor. The pyelograph will identify the cystic nature of the tumor in over half the cases. As I have previously described,* the pelvic outline of bilateral cystic kidney is characterized by flattening of the calices, giving a general oval contour to the pelvis in contradistinction to the retracted calices of the malignant renal tumor. Occasionally, however, a retraction of the calices may also be found with the bilateral cystic kidney, but it then is broad and open and not slit-like or narrow.

Tumor in organs adjacent to the kidney frequently cannot be identified even with the aid of all data obtainable through subjective symptoms, palpation, intestinal inflation, and analysis of stool, urine, and blood. Since about 20 per cent. of renal tumors have no definite history of disease in the urinary tract and a negative urinalysis, it is very evident that they may easily be confused with tumor in the adjacent organs and vice versâ. Cystoscopic data and particularly the pyelograph will identify or exclude renal involvement in about 75 per cent. of such tumors.

Closed pyonephrosis may be particularly confusing. The onset of a pyonephrosis may be most insidious, whether calcareous or tuberculous, and give the patient little or no subjective symptoms. The systemic toxemia as a result of such a pus-reservoir may give the appearance and systemic symptoms of malignancy. The tumor may feel as firm and irregular as a neoplasm. The cystoscopic examination discloses absence of secretion from that side and obstruction to the ureteral catheter at the renal pelvis, but the same condition may be found with malignant renal tumor. Data obtained by means of the pyelograph may be of considerable aid in such cases.

---

* Braasch: "Recent Developments in Pyelography," "Annals of Surgery," November, 1910, pp. 645–653.

Other Aids to Diagnosis

Cough.—A dry cough of comparatively recent origin, with negative chest findings, is suggestive of diaphragmatic irritation. While this may occur with various subdiaphragmatic tumors, it is found peculiarly frequent with renal tumor. Bronchial gland metastasis as a possible cause for cough was found in two cases. When this condition is suspected, the radiogram may show the metastasis, provided the bronchial glands are large and favorably situated.

Sex.—Renal tumor evidently occurs more often in the male than in the female. It was found in 51, or 62 per cent., of the males, and in 31 females.

Cystoscopic Data.—By means of the cystoscopic examination we can obtain data which, in most cases, will enable us definitely to determine the source of the hematuria, to ascertain the origin of pain, and to identify an otherwise symptomless tumor. These data will be gained through—(1) Inspection; (2) the ureteral catheter; (3) estimation of renal function; and (4) pyelography.

Cystoscopic Inspection.—The cystoscopic examination of the bladder may reveal—(1) Dilatation of the veins of the bladder; (2) tumor tissue loose in the bladder or protruding from the ureter; (3) blood-clot in the ureteral meatus; (4) atrophy of the affected meatus; (5) marked comparative decrease in volume and force of secretion; (6) unilateral dark-colored secretions; (7) unilateral hematuria. Dilatation of the veins of the bladder is seen only occasionally with conditions other than renal tumors and occurs usually as a result of mechanic pressure from an adjacent tumor. When found with tumor in the upper abdomen, it is strongly indicative of renal tumor. The dilated veins are not necessarily confined to the area surrounding the ureteric orifice, but may be found over the base and walls, more often on the affected side. While the secretion from the affected kidney may appear entirely normal, it not infrequently will have a comparatively dark brownish color, and its volume and force may be much less than from the other kidney.

Ureteral Catheter.—The data obtained by means of the ureteral catheter are secured through evidence of obstruction and dilatation. Obstruction to the ureteral catheter may result from—(1) Invasion and partial or complete obliteration of the renopelvis or upper ureter by tumor tissue, or (2) from pressure on the ureter by surrounding tumor tissue, particularly when the tumor is large and involves the lower pole. Some evidence of dilatation of the pelvis as a result of tumor changes may be obtained through the discovery of residual urine in the pelvis. Similarity of pain caused by pelvic overdistention is not to be relied on.

Estimation of Renal Function.—Evidence obtained through chemic estimate of decrease in renal function consequent to tumor must be considered with caution. With most renal tumors a quantitative functional estimate will not show a decrease sufficient for a definite estimate of disease. Although a considerable portion of the substance of the kidney may be invaded by tumor tissue, the remaining kidney will more often be found to secrete almost as great an amount as the entire kidney. When, however, the remaining renal tissue becomes involved in some secondary inflammatory process, as evidenced by pyuria, microscopic or macroscopic, the functional capacity will be markedly reduced. Since particularly those tumors in patients in whom the urine is found normal are difficult of identification, functional tests will be found to be of diagnostic value in but a small proportion. In 20 cases of tumor with urine containing no pus, marked decrease in function was noted in but 5. In these 5 cases but a very small amount of secreting tissue was found remaining. On the other hand, it must be remembered that pressure of an adjacent tumor on the kidney will diminish its functional activity, as measured by chemic tests. Various other circumstances may also cause a comparatively normal kidney temporarily to retard its secretory activity. Of the various functional tests, phenolsulphonephthalein will probably be found to be the most practical because of the simple technic involved and since it permits a comparatively accurate quantitative estimate.

Pyelography.—In over 75 per cent. of the kidneys operated on for malignant renal tumor the pelvis was found involved to a varying degree. Abnormality in pelvic outline consequent to such involvement can be demonstrated in the radiogram by injecting liquid solutions of silver colloid into the renal pelvis. In order to distinguish the normal from the abnormal, the outline

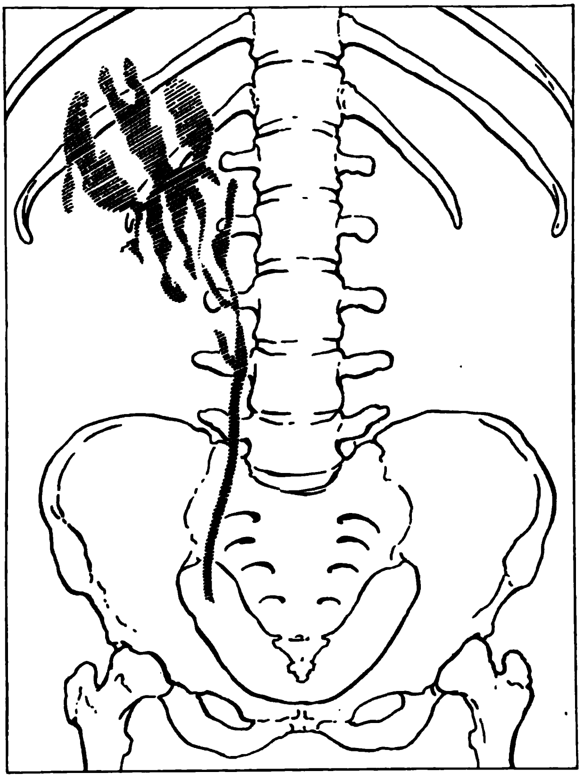


Fig. 83.—Typical "spider-leg" retraction of calices; note point of obstruction of catheter at level of fourth lumbar vertebra.

must vary considerably. In the 22 cases with operation in which pyelography was employed, recognizable deformity was demonstrated in 17. The changes in the pelvic outline as seen in the radiogram will be found to be as follows:

1. Retraction of one or more calices well into the cortex, giving a bizarre, "spider-leg-like" appearance (Fig. 83).

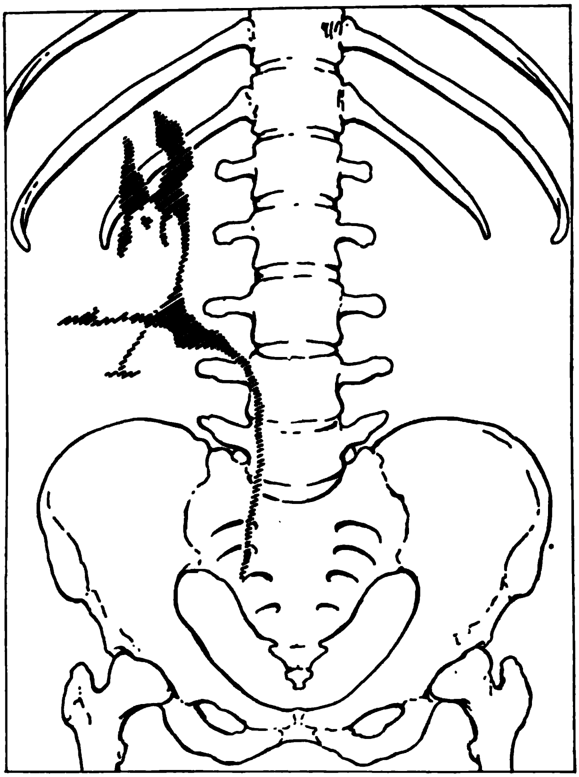


Fig. 84.—"Spider-leg" retraction of calices.

2. Partial obliteration of the pelvic lumen by invading renal tissue with remaining thin streaks (Fig. 84).

3. Irregular pelvic dilatation following tumor necrosis or secondary infection.

4. Retraction and consequent dilatation of the upper ureter by surrounding tumor.

5. Abnormal position of the renal pelvis so that its outline is found lying either extremely median or lateral (Figs. 85 and 86).

'Needless to say that pyelography should not be employed except when other means of diagnosis fail to identify the tumor.

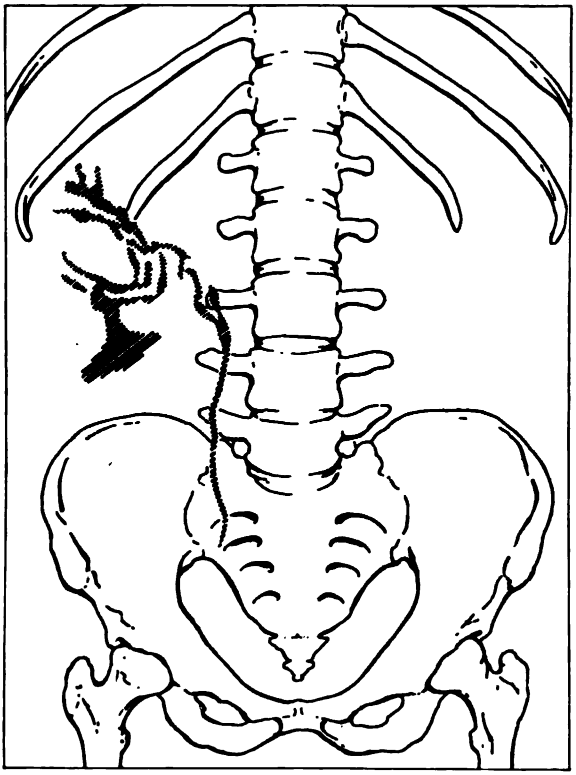


Fig. 85.—Typical retraction of calices into fine radiating streaks.

While it will cause no permanent injury, it occasionally will be accompanied by considerable pain unless carefully employed. It will be found particularly valuable in identifying renal tumor not accompanied by urinary symptoms, and in which urinalysis is found negative.

OPERATIVE FINDINGS AND RESULTS

Inoperable Tumor.—Among the 83 patients operated on for malignant renal tumor, the surrounding tissues were found so involved as to render nephrectomy impossible in 22. Among the 22 cases explored and found inoperable, the tumor was described as fixed in 16. Of the 22 patients, but 15 could be traced, and with 2 exceptions they were reported dead within a year after exploration. Our clinical records also show 21 patients in whom tumors in the zone of the kidney, hematuria, and other evidences of malignancy made the clinical diagnosis of malignant renal

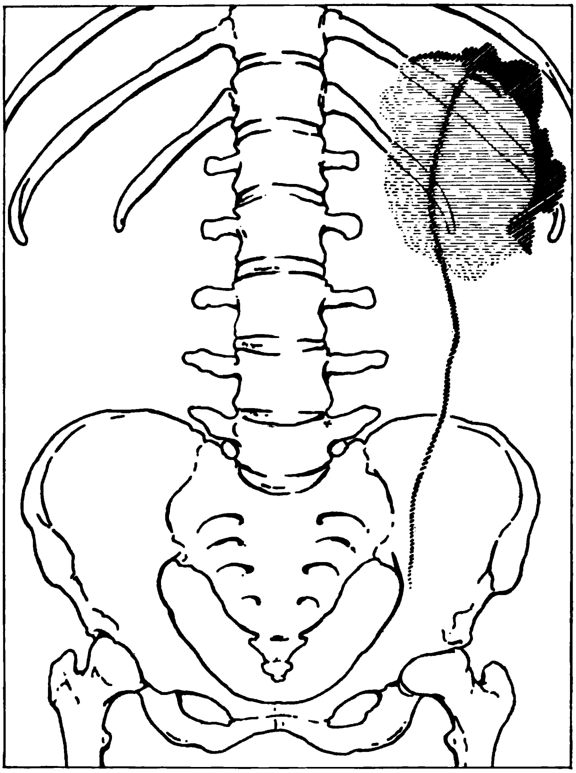


Fig. 86.—Flattening and lateral deviation of renal pelvis by median-lying tumor tissue.

tumor reasonably certain, but they were considered inoperable. Thus we have a proportion of 1 case in 5 considered inoperable clinically. This large proportion is not surprising, since the average duration of symptoms of the patients operated on was 2.3 years, while with 31 per cent. it was three or more years. The symptoms which caused us to consider the patient's condition as inoperable were—(1) Fluid in the abdomen; (2) edema of the extremities; (3) extreme emaciation and weakness; (4) evidence of metastasis; (5) cardiac insufficiency; (6) evidence of thrombosis. It must be remembered that metastases may be found when the

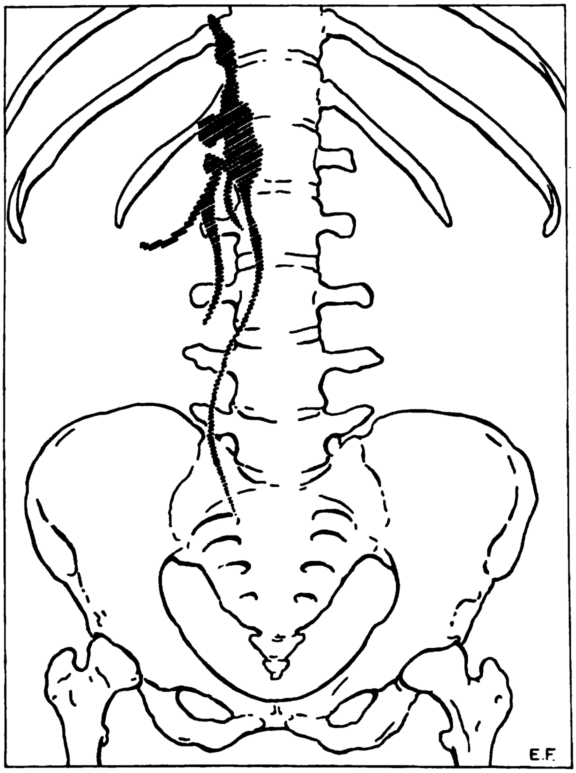


Fig. 87.—Flattening and median deviation of pelvis by lateral lying tumor, with retraction of calices.

renal tumor is so small that it cannot be palpated clinically. Microscopic sections of superficial tumors may be the first to call our attention to the existence of hypernephroma. In a case which came under our observation recently a metastatic tumor was found in the rectum.

Results of Nephrectomy.—Of the 61 patients in whom nephrectomy was done, 7, or 11 per cent., died in the hospital. Of the remaining patients, we were able to trace 51. Of these, 10 were operated on less than a year before, 17 were alive more than one year, 12 after three years, 4 after five or more years, and 1 after eight years. Of the 27 patients reported dead, 9 died before one year after operation, 2 lived one year, 4 lived two years, and 1 lived three, four, and five years after operation, respectively. Thus we have a three-year cure in 14, or 27 per cent., and a five-year cure in 5, or 10 per cent. Of the patients that were reported alive three years or more the average length of symptoms noted prior to operation was 1.6 years. Of those who lived less then three years the average length of symptoms was 2.8 years. It is evident, therefore, that, as a general rule, the shorter the existence of symptoms prior to operation, the better will be the prognosis. Furthermore, it is seen that results of nephrectomy for renal tumor compare favorably with operations for malignancy elsewhere in the abdomen.

In conclusion I wish to emphasize the importance of immediately ascertaining the source of every hematuria. Of the 53 patients operated on for malignant renal tumor who had a definite history of hematuria, but 18, or 34 per cent., had been advised to be examined for its source. Hematuria, particularly when so well marked as to color the urine, is always to be considered a sign of some grave condition in the urinary tract. In fact, it would be conservative to regard every case of hematuria as the result of a malignant process until it can be definitely proved otherwise. Renal tumor may lie dormant or grow insidiously over a period of years, and by the time that hematuria, tumor, or pain calls attention to its existence, it should receive immediate surgical attention.

THE EMBRYOGENETIC RELATIONSHIPS OF TUMORS OF THE KIDNEY, SUPRARENAL, AND TESTICLE *

LOUIS B. WILSON

INTRODUCTION

The urinogenital system presents more gross and microscopic anomalies than any other set of organs in the human body. This is because nature, in the development of these organs, pursues an indirect and wavering course. Nowhere else in the body are organs in the embryo first developed to a stage in which, like the mesonephros or Wolffian body, they present all appearance of being capable of active function, only to degenerate and have their remains utilized for the building of new structures, as the permanent kidney and testis. It is only by a study of the details of the intricate combinations and recombinations of the primitive factors which are used in the making of the urinogenital system that we shall come to understand in the adult either the gross surgical anomalies, or those more obscure aberrations which appear to contain the explanation of the puzzling tumors of the kidney and testis. The busy surgeon and the engrossed pathologist are both apt to overlook the enormous amount of accurate detailed observation which is being made by embryologists on the development of the urinogenital system. The last decad has seen an almost complete revolution in our ideas of the essential embryology of the system, and there are yet many obscure points which would appear to have a direct bearing upon its pathology. I wish herein to call attention to the chain of relations, to which

---

*Read before the Southern Surgical and Gynecological Association, December 19, 1912. Reprinted from "Annals of Surg.," April, 1913, pp. 522–535; "Trans. South Surg. Assoc.," 1912.

new links have recently been added, between the development of the organs in question and their pathology.

Huntington's Harvey[4] Lecture of 1907 gave so excellent a summary of the gross anomalies of the genito-urinary tract that it is unnecessary again to cover the field. I shall therefore confine myself to a consideration of the more minute embryologic anomalies which concern the development of tumors, based on a study of the operative and autopsy material from the Mayo Clinic, and consisting of the following:

Renal tumors	92
Adrenal tumors	3
Testicular tumors	21

This material has been supplemented also by a study of the human and comparative embryology of the regions under discussion.

RENAL TUMORS

In considering the embryologic relationships of the renal tumors, one groups them most conveniently into—(*a*) Tumors of the pelvis and collecting tubules; (*b*) tumors of the cortex; and (*c*) tumors of the capsule.

(*a*) *Tumors of the Renal Pelvis.*—Most of the tumors of the renal pelvis—papillomas and carcinomas—apparently arise secondarily to chronic irritative processes of the pelvic epithelium and have no embryologic significance. Our series contains 3 pelvic papillomas, all of the angiocystic type, developing in the collecting tubules in the apices of the Malpighian pyramids. The four renal carcinomas in our series have taken their origin similarly in the collecting tubules, and two of these are demonstrably superimposed on extensive renal calculus formation.

There is, however, one tumor of the renal pelvis in our series which is apparently of embryogenetic origin. (See Fig. 88.) This is a squamous-celled epithelioma, resembling histologically a cancer of the lip, and evidently derived from the ectoderm. The explanation of the presence of ectoderm within the renal pelvis in this case is as follows:

The renal pelvis, with its collecting tubules, develops from the primary excretory or Wolffian duct. The primary excretory duct is initially the excretory duct of the pronephros. It is developed from the principal tubules of the pronephros, which begin as evaginations of the mesoblastic parietal layer of each primitive segment stalk. It enters the cloaca low down on that structure, at a point close to its rectal portion. Before the opening occurs, however, the lumen of the cloaca may be seen to evaginate into the blind end of the primary excretory duct. It will thus be seen that, though the primary excretory duct is normally composed entirely of mesoblast, there is a possibility, as an abnormality, of ectodermal cells from the rectum being carried into its lower end by way of the cloacal wall. No other way appears by which one may account for the occasional though rare presence of these squamous-celled epithelial tumors within the renal pelvis.

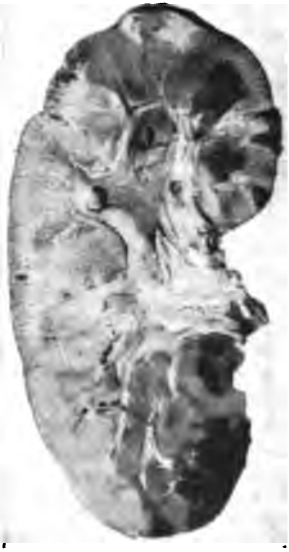


Fig. 88.—Case A 75112. Prickle-cell epithelioma of renal pelvis.

(*b*) *Tumors of the Renal Cortex.*—Occasionally a renal carcinoma, arising in the renal pelvis or collecting tubules, so involves the renal cortex that its pelvic origin cannot be positively determined. There are two such in our series. Occasionally also a renal sarcoma in the adult developing in a fibroma which has apparently had an inflammatory origin within the renal capsule may similarly so involve the renal cortex that its true point of origin is with difficulty made out. Much more rarely, I believe, do we have a primary spindle-cell sarcoma of the renal cortex arising from the adult connective tissue. There is but one of these of undoubted diagnosis in our series. This case is that of a girl sixteen years of age. As one reviews the literature, he is convinced that most of the renal tumors which have been diagnosed as sarcomas are in reality mesotheliomas or embryomas (Wilms'[3] tumors).

Our series contains two positively diagnosed and one doubtfully (exploratory operation) diagnosed embryomas, or Wilms' tumors, one of these occurring in a child two years (see Fig. 89) and the other two in children each five years of age. These tumors trace their embryologic relationship back to the formation of the nephrogenic cord, that portion of the mesothelium from the lower end of which is formed the secreting portion of the permanent kidney. In the very early embryo the mesoderm forms a wedge-shaped plate on either side of the medullary tube. This mesodermal plate early differentiates into three portions—a thick primitive segment (next the medullary tube), a constricted primitive segment stalk, and a thin lateral plate. The constricted primitive segment stalk furnishes the material from which the tubules of all three nephritic organs are developed. From the lateral plate are developed, among other things, muscle and cartilage. As the nephrogenic cord develops from the primitive segment stalk it is in immediate apposition to the bases of the lateral plates, and it is perfectly possible for tissue from the lateral plate area to be included within the formation of the nephrogenic cord. This is especially true in the caudal portion of the nephrogenic cord, which here lies closer to the lateral plate than it does in its middle and cephalic portions. Now it is from the extreme caudal portion of the nephrogenic cord that the cortex of the permanent kidney is developed. Accordingly, we should expect

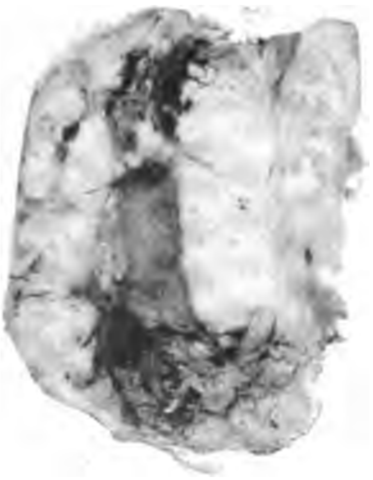


Fig. 89.—Case 15845. Embryoma of kidney from child two years of age.

to find here, if anywhere within the nephrogenic structures, inclusions of the lateral plate and subsequent developments therefrom of embryonic muscle, cartilage, etc. These are the structures which, along with other embryonic cells and tubules, give the diagnosis of the so-called mixed tumors of Wilms.

By far the most numerous tumors of the kidney are the mesotheliomas (so-called hypernephromas or Grawitzian tumors) of the renal cortex. (See Figs. 90 and 91.) I had the pleasure, three years ago,[12] of reporting before this society 32 cases of hypernephromas from the Mayo Clinic. Since then I have studied 22 more such cases from the clinic, making 54 in all, and tissues from 14 cases from the University of Minnesota clinic, or a total of 68 cases. Besides the 54 cases which have been diagnosed pathologically in our clinic, there are 17 cases which were diagnosed by the surgeon upon exploratory operation, making a total

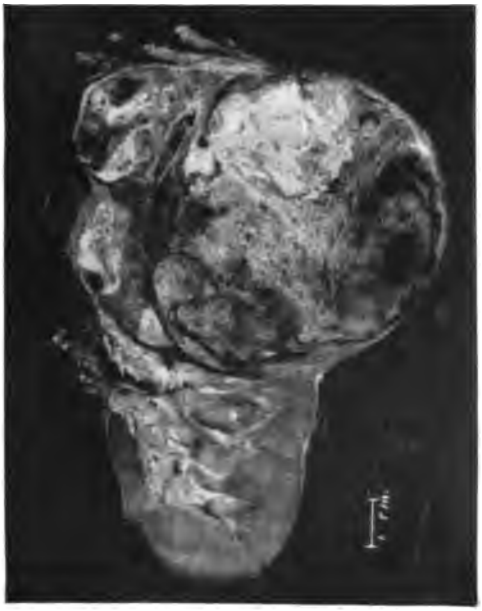


Fig. 90.—Case 64508. Mesothelioma of upper pole of kidney.

of 71 cases of mesothelioma out of a total of 92 renal tumors, or 78 per cent. of all tumors of the kidney removed.

Grawitz's hypothesis of the derivation of these tumors from adrenal rests was based upon the following: (1) The tumors are situated immediately beneath the capsule of the kidney. (2) Their cells are different from those of the epithelium of the uriniferous tubules. (3) The cells contain fat, which is normally absent from the renal epithelium, but frequently present in the suprarenal epithelium. (4) The capsule of the tumor is similar to that which is found around suprarenal rests within the kidney, but which are not changed into tumors. (5) The cells of the tumors are sometimes disposed in more or less regular cordons, which resemble those of the suprarenal cortex.

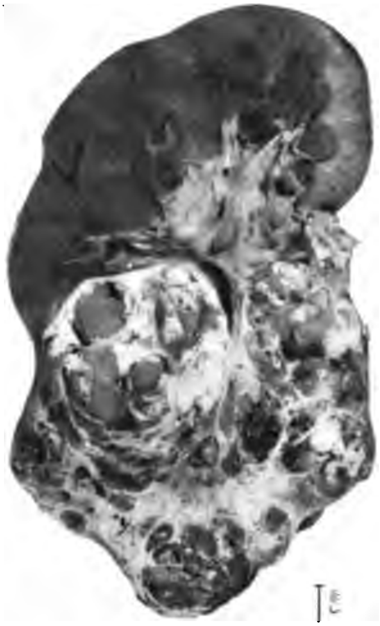


Fig. 91.—Case 60651. Mesothelioma of lower pole of kidney.

Grawitz's hypothesis was accepted by most observers during the next quarter of a century following its formulation. During this time it was attacked by Sudeck,[2] and finally quite effectively by Stoerck,[6] who showed that:

(1) The Grawitzian tumors most frequently develop at the lower pole of the kidney, where adrenal rests are not found.

(2) The so-called fat of the cells of the Grawitzian tumors is usually not fat, but a vacuolation related to the glycogen content of the cells.

(3) The Grawitzian tumor is a tumor of the renal cortex, and not of the renal capsule, in which adrenal rests are usually found, and that—

(4) Though the Grawitzian tumors do frequently contain cordons, which, however, only remotely resemble those found in the suprarenal, yet they also almost invariably contain tubules, the analogues of which are never seen either in the normal suprarenal or in the tumors of that gland.

Stoerck's very convincing evidence and arguments against the Grawitzian hypothesis I have been able fully to support by a study of our own cases, as have also the observations of Jelle,[7] Trotter,[8] Zehbe,[10] Sisson,[11] and Glynn.[15]

It has seemed to me from the first, however, that there are serious objections to Stoerck's suggestion that these neoplasms arise from regenerating convoluting tubules in the atrophic kidney. After a careful study of the embryology of the kidney and of the histologic structure of 48 cases, I proposed, three years ago,[13] the hypothesis that these tumors are really derived from islands of nephrogenic tissue which have failed to become connected with the renal pelvis, through the collecting tubules, of the developing kidney.

It will be recalled that, as the primitive renal pelvic bud—derived from the primitive excretory (Wolffian) duct—grows dorsally from its point of origin, it is surrounded by a cap of mesothelial tissue, the metanephrogenic cord, which is the caudal extremity of the mass of mesothelium from the forward end of which has been previously elaborated the Wolffian body. After the first two or three branchings of the renal pelvis, at each later subdivision for the elaboration of the collecting tubule system this cap of nephrogenic tissue is separated into masses, one of which remains surrounding the terminus of each of the growing collecting tubules. In the later subdivision of the tubules masses of the nephrogenic tissue are also left in the angles of the branching tubules. The nephrogenic cells of each of these small masses soon arrange themselves as an oval or spheroid about an eccentrically placed point, which soon becomes a cavity, thus making of the cell mass a small, elongated, ovoid vesicle. This vesicle then becomes fused at its lesser extremity with the end of the collecting tubule. From the vesicle are normally formed the renal glomeruli, the convoluted tubules, the loop of Henle, and the uriniferous tubules, up to the straight collecting portion which is derived from the primitive renal pelvic bud.

For a long time it has been considered that the failure of the nephrogenic vesicles to form a tubular connection with the collecting tubules is responsible for the condition of congenital cystic kidney. A study of the development of the nephrogenic vesicle, however, has convinced me that such a failure in its embryonic development is responsible for much more than the formation of renal cysts. Primarily, the nephrogenic cap consists of somewhat darkly staining, round, and irregularly arranged embryonic cells. In the first stage of the formation of the vesicle it is a solid mass of cells, which is frequently somewhat elongated, and presents a cordon-like appearance. In its second stage it is first an ovoid vesicle and then a tubule. Now all these embryonic pictures closely resemble those which we find making up the histologic elements of the Grawitzian tumors. I have therefore urged the hypothesis that these tumors are mesotheliomas or, more definitely, nephromas; that is, that they are elaborated from masses of nephrogenic tissue which have never become connected with the renal pelvis and which have never attained adult type in either form or function. In fact, I feel sure that, as the evidence continues to accumulate, it will show first that the so-called Grawitzian tumors have nothing whatever to do with a suprarenal origin, and, second, that they are true mesotheliomas (nephromas) arising from masses of nephrogenic tissue, the normal embryologic development of which has been arrested or perverted *after* the beginning of the development of the kidney proper.

(*c*) *Tumors of the Renal Capsule.*—That the renal capsule is not infrequently the site of tumors forming in its adult tissue is well demonstrated. Fibromas, and in their wake spindle-cell sarcomas, are not rare. Our series contains one of the former and two of the latter type (see Fig. 92), all arising in adults beyond thirty-five years of age. These sarcomas of the renal capsule are apt to invade the renal cortex and be mistaken for tumors arising in this portion of the organ.

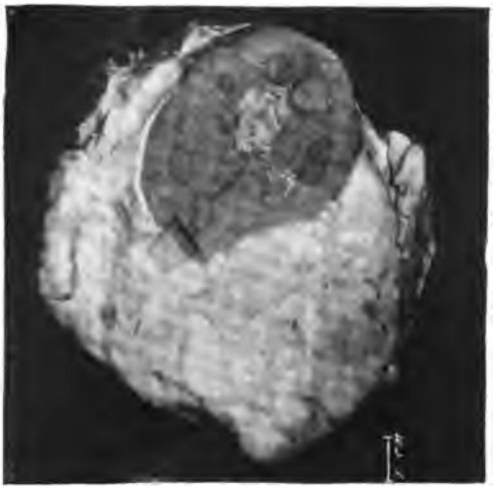


Fig. 92.—Case A73091. Transverse section of kidney with spindle-cell sarcoma arising in capsule.

As far as its embryologic relationships are concerned, the renal capsule is frequently the site of inclusions from the mesonephros, Wolffian body, and occasionally, though rarely, of inclusions from the suprarenal. The beginnings of the renal capsule are seen as embryologic connective tissue concentrically arranged about the embryonic kidney as early as in 13 mm. embryos, though the actual capsule, well differentiated from the surrounding tissue, is not observed until we reach 70 mm. embryos. In the early stages of capsular development the degenerating tubules of the Wolffian body lie in immediate apposition to, or indeed commingled with, the embryonic connective-tissue fibers which enter into the formation of the capsule. Consequently, the inclusion of masses of the degenerating Wolffian tubules in the renal cortex is very easily understood. We have in our series one well-marked case of this type, that is, an encapsulated mass of Wolffian tissue lying within the renal cortex.

Though it is true that undoubted inclusions of suprarenal tissue have been found in the renal cortex, I am convinced that they are much more rare than they are usually supposed to be. Several pathologists with an extensive postmortem experience state specifically that they have never personally observed a single instance. Glynn,[15] in a recent careful survey of the literature, has collected 17 cases, to which he adds 2 cases of his own. To these we may add 1 case from our autopsy records. They are usually well encapsulated, though at least one instance has been reported in which there was no visible connective tissue between the mass and the structure of the kidney.

Glynn[15] notes the following facts opposed to the hypothesis that adrenal hypernephromas arise from the remnants of adrenal cortex:

(*a*) The histologic dissimilarity between tumors of the renal and adrenal glands.

(*b*) Renal tumors never influence growth of sex characters.

(*c*) Why should adrenal rests, though comparatively rare in the kidney, produce hypernephroma, the commonest renal tumor, while adrenal rests in other localities, though comparatively common, so rarely produce tumors, either benign or malignant?

While it is perfectly conceivable that such masses within the renal cortex may form malignant neoplasms, I find neither in the literature nor in my own experience any evidence that such is the case. Should such tumors form, they must, to satisfy the present demands of diagnosis, conform to the histologic type of those tumors which we know to be primary in the suprarenal. In other words, it is but fair to assume that a neoplasm derived from wandering suprarenal cells will present the same histologic elements as neoplasms derived from suprarenal tissue in its normal position.

TUMORS OF THE ADRENAL GLAND

The well-known fact that the cortex and medulla of the suprarenal are derived from different embryologic structures accounts for the great diversity of tumors of this gland. The medulla is chromatin tissue derived from the sympathetic nervous system, and the cortex is derived from the celomic epithelium. Glynn[15] has recently reviewed the pathology of the rests and tumors of the adrenal cortex. His summary and conclusions in part are as follows:

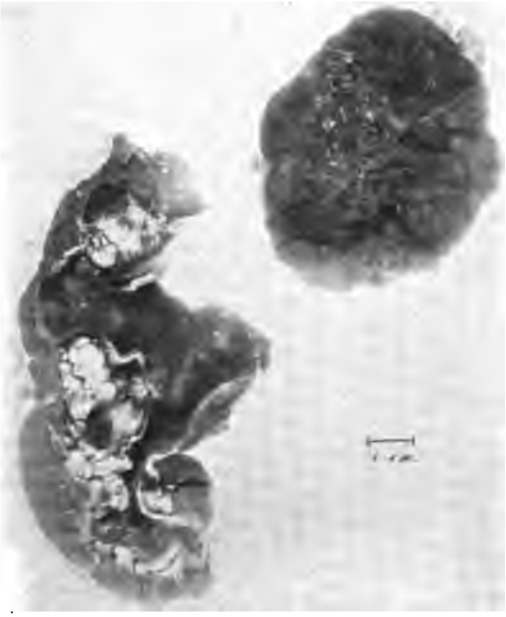


Fig. 93.—Case A66865. Adenoma of suprarenal. Longitudinal section of kidney and tumor.

1. "Tumors (of the adrenal) are rare, especially primary malignant tumors, which are represented by (*a*) round-cell

sarcoma and (*b*) adrenal hypernephroma; an epithelial growth of cortical origin."

2. "Adrenal hypernephromas are associated with sex abnormalities almost invariably in children, usually in adult females before the menopause, but apparently never in adult females after the menopause, or in adult males."

A recent study of three tumors of the suprarenal which have come to our clinic is additional evidence to the above. The first of these tumors of the suprarenal was in a woman (Case A66865), forty-one years of age, who for fourteen years had had hematuria at irregular intervals, with pain in the right kidney, accompanied recently by dysmenorrhea and considerable loss of weight. A clinical diagnosis of hematuria from chronic infection of the renal pelvis was made. At operation the right kidney (see Fig. 93) was found with a very thin cortex, and a distended pelvis the seat of chronic inflammation and giving abundant

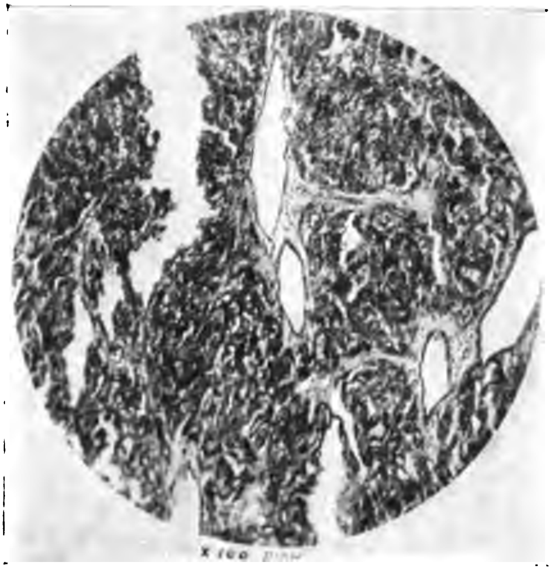


Fig. 94.—Case A66865. Adenoma of suprarenal (photomicrograph × 100 diam.).

evidence of the hematuria. An encapsulated tumor as large as a hen's egg was found above the kidney, but pressing somewhat upon the ureter. Histologic examination of this tumor (see Fig. 94) shows it to be an adenoma of the adrenal cortex.

The second case was a man, forty-seven years of age, who, like two cases quoted by Glynn,[15] had been noted for years for his enormous strength. He had been perfectly well until three months before the examination, when, after great exposure on a five days' tramp through slush and snow in Alaska, he developed pain and a tumor mass in the epigastrium. When brought to the clinic there were multiple tumor growths over his trunk, head, and neck. One of these from the axilla was excised, and on histologic examination a tentative diagnosis of hypernephroma was

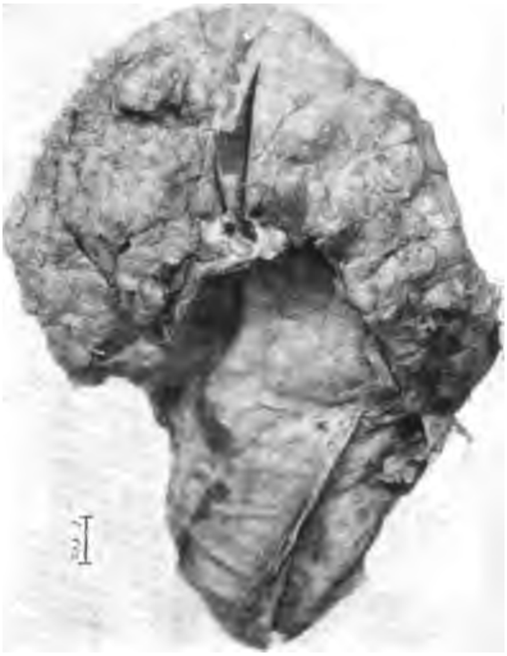


Fig. 95.—Case A72057. Hypernephroma of adrenal.

made. The disease steadily progressed, and the patient died four months after the onset of symptoms. Autopsy revealed large tumors occupying the position of each suprarenal. (See Fig. 95.) There were small metastatic nodules in each kidney, many large ones in the omentum, in the spleen, in the liver, in the heart-wall, in the lungs, and in the lymphatics generally throughout the body. A careful histologic study of this tumor (see Fig. 96) shows it to be composed almost entirely of large polyhedral cells with some multinucleated giant forms and a few smaller round-cells—a typical hypernephroma of the adrenal cortex.

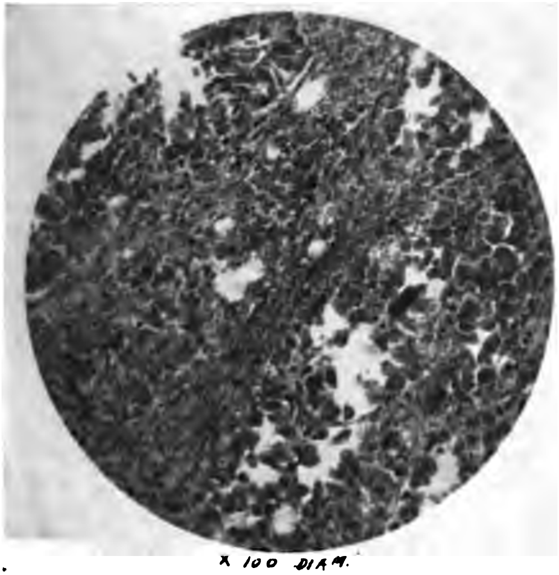
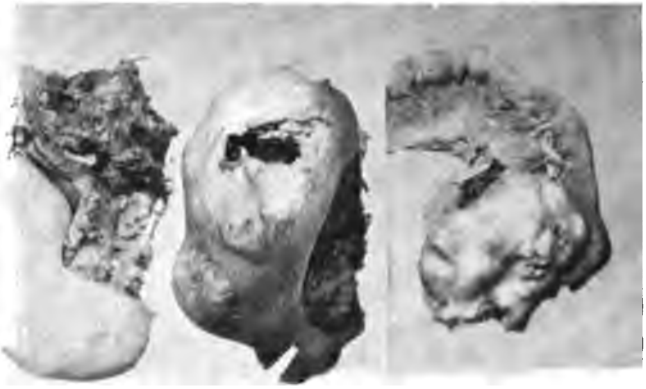


Fig. 96.—Case A72057. Hypernephroma of adrenal (photomicrograph × 100 diam.).

The third case was a man, sixty-eight years of age, who had had "stomach trouble" for four months. Surgical exploration revealed numerous small tumors of the peritoneal glands and small intestine. The patient died four days later of pulmonary embolism. Autopsy revealed large necrotic tumors (see Fig. 97) completely involving both suprarenals, with metastases to the



Kidney and Adrenal Spleen Metastatic Tumor of Ileum

Fig. 97.—Case A75198. Hypernephroma of adrenal, with metastases to spleen and ileum.

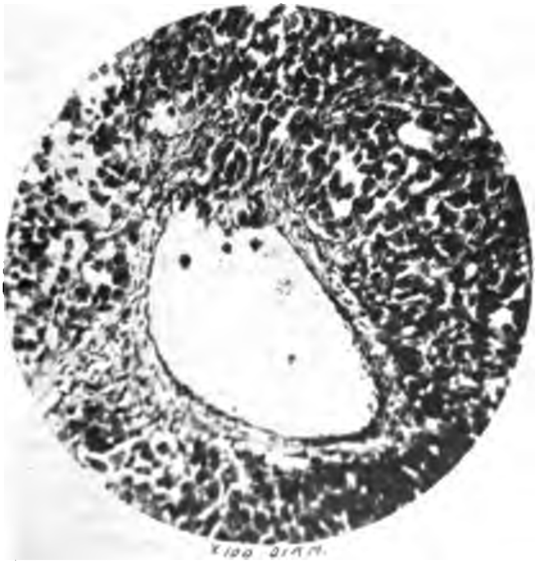


Fig. 98.—Case A75198. Hypernephroma of adrenal cortex (photomicrograph × 100 diam.).

peritoneal glands, small intestine, spleen, and liver. Microscopically (see Fig. 98) the tumors are large, round, and polyhedral celled hypernephromas of the adrenal cortex.

These three hypernephromas of the adrenal cortex form an interesting series for comparison with the so-called hypernephromas of the renal cortex. The first case still recognizedly preserves the cordon structure of the adrenal cortex, and yet one would not hesitate to differentiate it from the cordons found in renal tumors. The two latter cases, which were far advanced and are parallel in their stage of development with most of the renal tumors in our series, have lost almost entirely all evidence of cordons. Their cellular structure, however, could not by any possibility be mistaken for any of the pictures found in our series of renal tumors. It is also especially interesting to note that the fat content of the cells of the adrenal tumors is very high, not only in the primary tumor, but also in the metastases, including those in the kidney itself. This is in marked contrast to the absence of almost if not all the fat in the cells of renal tumors.

While these adrenal hypernephromas are of particular interest to the clinician in the light which they throw on the functions of the adrenal in relation to sex development, they are of quite as great interest in the negative evidence which they supply concerning Grawitz's hypothesis of the suprarenal origin of renal tumors.

TUMORS OF THE TESTICLE

Ewing's[14] article on tumors of the testis about two years ago, March, 1911, has left little room for discussion unless based on evidence furnished by new material. In brief, Ewing[14] concludes:

"(1) Pure fibromas and pure leiomyomas of the testis exist, but are extremely rare, as is also adenoma occurring in atrophic undescended testes."

"(2) Primary lymphosarcoma and pure spindle-cell sarcoma are of uncertain origin."

"(3) Chondroma, myxoma, lipoma, rhabdomyoma, and carcinoma have not been shown to exist apart from a teratomatous origin."

"(4) Alveolar large round-cell perivascular and other forms of so-called sarcoma testis are of epithelial and teratomatous origin."

"(5) The commonest tumor of the testis is an embryonal carcinoma, alveolar or diffuse, with polyhedral or round-cells, and often with lymphoid stroma. These tumors are probably one-sided developments of teratomata."

"(6) Teratoma testis arise from sex cells in the neighborhoods of the rete, whose normal development into spermatogonia has been suppressed, but whose potencies remain intact and ready to express themselves in the various forms of simple or complex teratomas."

Our series of tumors of the testicle contains 21 cases, 2 of which were exploratory only, each apparently a sarcoma of an undescended testicle. The histology of the other 19 cases has been studied in detail. Though the specimens vary a great deal in their relative cell content, every one of them would undoubtedly be classed as a teratoma by Ewing.[14] Eleven of the 19 are alveolar embryonal carcinomas (see Fig. 99), with rounded or polyhedral cells, 5 show cartilaginous and 7 myxomatous tissue with their structure. From a clinical standpoint it is somewhat interesting to note that 6 of the 19 cases give a history of injury definitely related to the onset of symptoms in the injured testicle.

Ewing's[14] hypothesis is that these teratomas of the testicle arise from sex cells whose normal development has been suppressed. This is interesting in relation to the recently published observations of Felix[16] on the presence of wandering genital cells in early human embryos. Felix[16] has found, in a careful search of all the tissue in a human embryo of 2.6 mm. (13 pairs of primitive segments), 7 genital cells, all in the immediate vicinity of the cloaca, and all between it and the visceral mesoblast. In an embryo of 2.5 mm. (23 primitive segments) he found 12 primary genital cells in the same locality. Felix[16] observes that "if these wandering genital cells are strays, they perhaps do not degenerate, but may further develop, and above all divide, forming parent cells for tumors and especially for teratomas."

The genital cells are the most important cells of the reproductive glands. Until recently embryologists described their derivation from the cœlom. Recently, however, much evidence has been accumulating that their origin is directly from the segmentation of the ovum, and it is possible that the future sex of all the genital cells is already determined at fertilization. Whether these genital cells differentiate into spermatogonia or oögonia is still unsettled. On the other hand, it is readily determined that

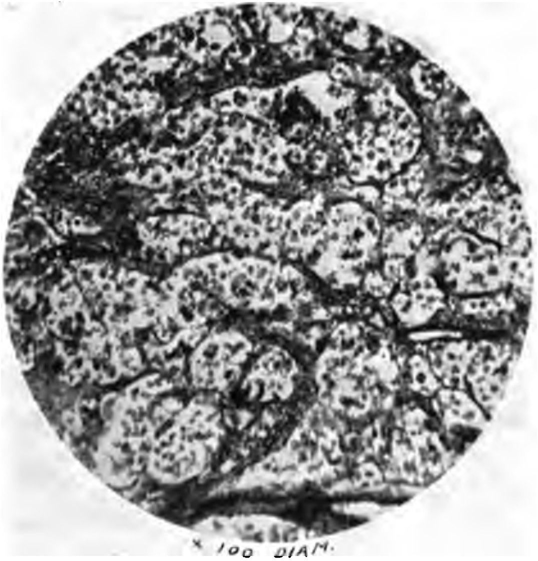


Fig. 99.—Case A39407. Teratoma ("alveolar carcinoma") of testicle (photomicrograph, × 100 diam.).

the indifferent reproductive gland does change into testis or ovary, as the case may be. In the male, this change is clearly shown in 13 mm. embryos. It consists of the appearance of anastomosing epithelial cords and the development of the tunica vaginalis between these cords and the surface epithelium. The cords of the testis are initially composed of indifferent epithelial cells with darkly staining nuclei. The genitaloid cells lie irregularly between these. They are found present at the time of the earliest appearance of the cords. Some of the genitaloid cells by the time the embryo has reached 70 mm. in length have developed into genital cells. Branca and Bresseta[5] have shown that, while the number of genital cells in the testicle increases up to birth, after birth they entirely disappear and the tubules of the testis contain indifferent cells only. At puberty a new growth of genital cells is developed, and from these are formed the spermatozoa. Popoff[9] has confirmed these observations, which seem to have an important bearing upon Ewing's[14] hypothesis of the formation of testicular teratomata from genitaloid cells. This wide gap between the genitaloid cells of the embryo and those which form at puberty may account for the great variation in type and speed of development of the teratomas of the testicle.

SUMMARY

Renal Tumors

1. Of 92 renal tumors studied, there were 3 pelvic papillomas, 4 carcinomas, 1 squamous-cell epithelioma, 1 adenoma, 1 fibroma, 7 sarcomas, 1 Wolffian tumor, 3 embryomas (Wilms'[3] tumors), and 71 mesotheliomas.

2. The renal papillomas and carcinomas apparently arise secondarily to chronic irritative processes of the adult pelvic epithelium.

3. The rare squamous-cell epithelioma probably is a neoplastic development from the embryonic inclusion within the renal pelvis of ectoderm, which has found its way into the lower end of the primitive excretory duct by way of the cloaca.

4. The embryomas of the renal cortex, composed of renal and other tissues and occurring in young children, are, according to Wilms,[3] derived from inclusions of thel ateral embryonic plate within the caudal portion of the nephrogenic cord in the early embryo.

5. The most numerous tumors of the renal cortex, the so-called hypernephromas or Grawitzian tumors, are apparently

mesotheliomas derived from nephrogenic vesicles which have failed in the early embryo to form a tubular connection with the renal pelvis.

6. Most of the few true sarcomas of the kidney develop primarily in adult tissue of the renal capsule and involve the cortex secondarily.

7. The renal cortex is also frequently the site of inclusions from the mesonephros, and rarely of inclusions from the suprarenal gland. Rarely, if ever, do either of these inclusions in the renal cortex form malignant tumors.

Adrenal Tumors

8. Of the 3 primary tumors of the adrenal studied, 1 was an adenoma and the other 2 hypernephromas of the adrenal cortex.

9. Primary malignant tumors of the adrenal are either round-cells sarcomas or more frequently hypernephromas arising from the adrenal cortex.

10. Adrenal hypernephromas frequently induce abnormalities of sex and strength.

11. Tumors of the adrenal, in whatever stage of their development, bear no histologic resemblance to most mesotheliomas (so-called renal hypernephromas).

Testicular Tumors

12. Of the 21 tumors of the testicle, all of the 19 which it was possible to study in histologic detail were teratomas.

13. So far as can be determined, the history and histology of these 19 cases are in harmony with Ewing's[14] hypothesis that teratomas of the testicle arise from sex cells whose normal development has been suppressed.

14. The difference in time of development of the embryonic crop of genitaloid cells and the next generation which appears at puberty may account for variations in structure and *tempo* of the testicular teratomas.

REFERENCES

1. Grawitz: "Virchow's Archiv," 1883, vol. xciii.
2. Sudeck: "Virchow's Archiv," 1893, vol. cxxxiii, p. 407.
3. Wilms: "Die Mischgeschwülste," Berlin, 1902.
4. Huntington, G. S.: "The Harvey Lectures," 1907, pp. 222–267.
5. Branca and Bresseta: "Arch. gén. de Chir.," 1907, vol. i, pp. 116–124.
6. Stoerck: "Beit. z. Anat. u. allg. Path.," 1908, vol. xlii, pp. 393–437.
7. Jelle: "Bull. et Mém. de la Soc. Anat. de Paris," 1909, sixth Ser., vol. vii, 11, No. 4.
8. Trotter: "London Lancet," 1909, vol. ii, pp. 1581-1586.
9. Popoff: "Arch. de Biologie," 1909, vol. xxiv, pp. 433–500.
10. Zehbe: "Virchow's Archiv," 1910, vol. cci, p. 150.
11. Sisson: "Ziegler's Beit.," 1910, vol. xlix.
12. Wilson: "Old Dominion Jour. Med. and Surg.," 1910, vol. x, pp. 237–252.
13. Wilson: "Jour. Med. Research," 1911, vol. xxiv, pp. 73–90.
14. Ewing: "Surg., Gyn. and Obstet., 1911, vol. xii, pp. 230-261.
15. Glynn: "Quarterly Jour. of Med.," 1912, vol. v, pp. 157-192.
16. Felix: Keibel and Mall's "Human Embryology," 1912, vol. ii, p. 884.

THE FUNCTION OF THE URETEROVESICAL VALVE *

AN EXPERIMENTAL STUDY OF THE FEASIBILITY OF URETERAL MEATOTOMY IN HUMAN BEINGS†

JOHN WILLIAM DRAPER AND WILLIAM F. BRAASCH

The idea of removing ureteral calculi by slitting the ureterovesical valve is not new. From the point of view of physiologic surgery, however, the relative value of this valve to the animal economy has not yet been made clear. Alexander Pappa says: "Direct-vision cystoscopy makes it possible for the operator to seize the calculus which shows in the bladder, makes possible also the enlargement of the ureteral meatus, and even occasionally the incision of the meatus on the stone which enables it to be liberated." In the discussion of an operation for prolapsed ureter, Albarran states: "The bladder having been opened through a hypogastric incision, one cut of the scissors enabled me to section at once both the upper margins of the ureteral orifice and the bladder wall for the distance of a centimeter." It will be noted that this work was done from above rather than through a cystoscope. Albarran further says: "The results of the operation were not so good so far as affording symptomatic relief. A second cystoscopic examination was therefore made and the orifice of the ureter operated on was seen to be enlarged and passing urine in very feeble jets." The significance of this statement and its relations to Cathelin's views will be referred to later.

---

* Read in the Symposium on Renal Surgery and Pathology in the Section on Genito-urinary Diseases of the American Medical Association, at the Sixty-third Annual Session, held at Atlantic City, June, 1912.

† Studies from the Laboratory of Surgical Chemistry and Physiology, Mayo Clinic. Reprinted from "Jour. Amer. Med. Assoc.," January 4, 1913, pp. 20-27.

Thompson reports having incised the mucous membrane of the bladder for the transvesical removal of a stone from each ureter with success. Wulff reports a case in which a ureteral calculus was removed by means of galvanocauterization of the ureteral orifice.

Kropeit removed stones which had lodged at the ureteral orifice in two cases. In the first patient he was able to effect the removal by means of the operative cystoscope. In the second, the stone could not be grasped by the forceps and he therefore slit the ureteral valve by means of the galvanocautery. Two days later the calculus was discharged spontaneously.

Kelly has demonstrated the feasibility of operating on the vesical end of the ureter by means of forceps and sounds through his female cystoscope.

Bransford Lewis has reported the removal of a number of calculi by means of his operative cystoscope.

One of us (Braasch) has removed ureteral calculi in 16 instances through the operative cystoscope by dilatation of the ureteral orifice and by means of manipulation through the use of ureteral sounds or catheters.

W. J. Mayo has, by transvesical operation, removed stones by manipulation and dilatation of the ureter through the bladder.

While such dilatation of the meatus and manipulation of the ureter with sounds, etc., will dislodge a small proportion of ureteral stones, there will be a large proportion which will require actual incision of the ureter to remove them.

In general, however, the literature bearing on actual section of the valve is very sparse. Actual section of the valve, particularly through the operative cystoscope, in the occasional instances in which it has been practised, appears to have been done on the spur of the moment without much opportunity for forethought or afterthought by scattered observers whose final results have not yet been tabulated. Immediate operative success is in itself no guarantee or safeguard against remote injury due to operative destruction of structures which may be necessary to the maintenance of metabolic equilibrium or for the mechanic protection of local regions. If the general views as to the importance of the protective mechanic function of the ureteric valve are to be accepted without qualification, its destruction would certainly appear to be so serious a matter that operators would naturally hesitate to slit it in preference to opening the ureter from above.

The fact, however, that but a single immediate fatality due to intraperitoneal leakage from the bladder and no chronicle at all of serious after-results has been found reported in the literature by us has seemed to point definitely to the immediate safety of meatotomy. This fact, together with the knowledge that in recent years a great deal of important new information has been elicited regarding the physiology and pharmacology of the ureter which appears to have important bearing on the applied surgery of the bladder, led us to begin these experimental studies. It tended also to make the portion of the study relating to the immediate operative danger more or less corroborative in character, the final trend of the research being directed rather toward an interpretation of the possible remote results of meatotomy should any be observed.

Safety of Ureteral Meatotomy

The problem regarding the safety of ureteral meatotomy in human beings resolves itself into the following terms: (1) Is it a safe procedure from the point of view of hemorrhage and sepsis due to accidental perforation of the bladder? (2) What ill result, if any, is to be expected from the destruction of the valve and the loss to the individual of its mechanic function? The latter question is further divisible into two: (*a*) Danger from ureteral reflux, dilatation and accompanying ascending infection; (*b*) danger of a remote character associated with the impairment of kidney function due to changes in intra-ureteric and renal pelvic pressures.

In the human being there is no artery of normal distribution in the valve which is of sufficient size to be worthy of consideration. This has also been observed true in our experiments in the dog. The chance of an aberrant artery crossing the valve in such a position as to be cut is also so remote as to be negligible. The valvular blood-vessels in the human bladder consist largely of a venous plexus which surrounds the vesical termination of the ureter and which may be a continuation of the well-known plexus which surrounds the bladder. These histologic studies of the ureteric valve served to strengthen the impression already gleaned from the operative experience of others that the probability of immediate or remote hemorrhage from cutting the valve either in man or in dog is so slight as to be negligible.

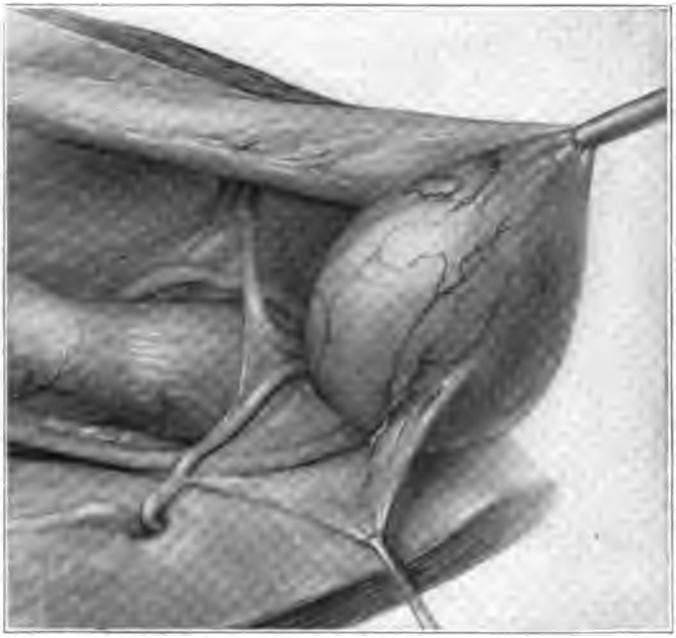


Fig. 100.—Bladder of dog pulled outward to show the vesical extremities of the ureters and extent of peritoneal covering.

The peritoneal investiture of the vesical extremity of the ureter as well as the blood-supply of the part in the dog present such anatomic conditions (Fig. 100) as to make if difficult without great carelessness to slit the ureteric mouth so far as to penetrate the bladder-wall. A well-defined sheath, which in its caudad

2 or 3 cm. is a very dense and fibrous structure, surrounds the dog's ureter. As regards the anatomy of the part in the human being, it closely resembles that of the dog. Piersol, quoting Waldeyer, says: "The last 18 mm. of the renal duct are embedded within the vesical wall; the muscular tissue of the latter is seemingly prolonged over the ureter outside of the bladder for some 5 mm. as a distinct sheath. Beginning several centimeters above the bladder, the adventitia of the ureter is strengthened by longitudinal bundles of involuntary muscle, that follow the duct to its vesical orifice and in conjunction with the fibrous tissue in which they are embedded, form the ureteral sheath." Following Disse, Piersol considers that "this muscle belongs to the wall of the ureter and is distinct from the musculature of the bladder."

In regard to the valve he says:

> "As the oblique course of the ureter . . . leaves it on the inner aspect covered by mucous membrane only, and as the outer aspect is covered by the muscular layer of the bladder-wall, it can be understood that the incision of the mucosa over the intraparietal part of the ureter, for the purpose of extracting a calculus, involves little risk of pelvic cellulitis from extravasation of urine. It cannot be said that there is no risk, as in one case a parietal fistula was established and death resulted."

It has seemed to us, from a study of the very thick-walled dog's bladder, that there occurs a great variation in the course and obliquity of the vesical portion of the ureter depending on the degree of dilatation or contraction of the bladder. This organ is subject to continual changes in size, as Howell states, owing to the fact that "every physical act and every sensory stimulus is apt to cause a contraction." This fact is also well known to every cystoscopist who has met with an anatomic or physiologic obstruction to the ureteral catheter at this point. As the bladder dilates, the size of the opening just at the point of entry through the mucosa is apparently not so much affected owing to the oblique insertion as it would be if the entrance were direct. It may well be that this is one of the reasons for and uses of the oblique insertion.

Experimental Technic

The method which we have found satisfactory for cutting the ureters in dogs is a simple one. It was devised by Abbott in this laboratory (Mayo Clinic). Prior to its employment we were much troubled by oozing from the bladder. This is apt to be quite free if the epithelium be traumatized by even a gentle touch of the finger. Considerable traction may be made on it in using Dr. Abbott's method of evagination without causing this annoying sequel.

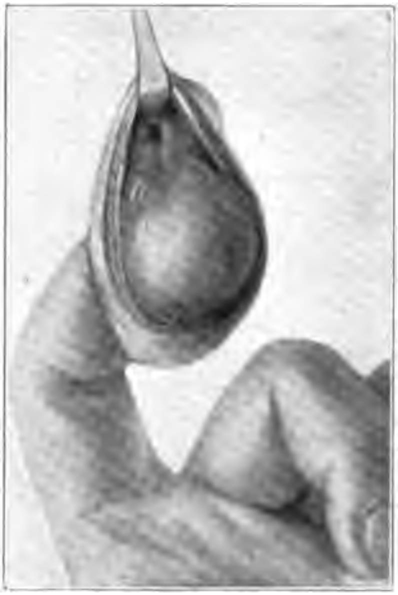


Fig. 101.—Mesoventrad incision in bladder showing Abbott's method of exposing trigone without traumatism to mucosa.

All animals were operated on under complete ether anesthesia. The bladder was opened by a median ventrad incision about 2 cm. in length, having its point of origin well toward the neck of the bladder. The viscus was then evaginated on the operator's index-finger, which is applied to the dorsal surface (Fig. 101). By this procedure the ureteric slits were usually brought into plain view and could be cut out with a small pair of slender-bladed scissors. Great care should be taken not to handle the mucosa or to bruise it in any way because even the most delicate touch is apt to cause it to become obscured. We have usually cut the valve until the tip of the scissors-blade was felt to be distinctly against the wall of the bladder. The incision thus made has in our experience averaged slightly less than 1 cm. in length and it has never approached dangerously near to the peritoneal aspect of the bladder.

The slitting of the meatus was done suprapubically because of its being difficult to do the operation on a dog through a cystoscope. The dog's bladder is so contractile that it requires much more water-pressure to distend it than in the case of the human bladder. Ordinary operative cystoscopes do not work favorably under this increased pressure, and the valve cannot be conveniently cut in a contracted bladder.

In order to obtain a series in which chronic cystitis had existed in conjunction with slit valves, we introduced an insoluble foreign body into the bladder just after the valves had been cut. Just prior to introduction this was thoroughly infected with colon bacilli and other organisms of autogenous origin. The presence of such a foreign body within the bladder appears to be necessary in order to create conditions which bear resemblance to the symptom-complex of human cystitis. In general no difference was to be observed clinically between the animals which had infected bladders and those in which no insoluble material was used. Although pus-cells and micro-organisms were present in urine which was removed under sterile conditions from all the bladders subjected to this foreign body treatment, the histologic findings in the kidneys were as negative in the infected series as in the uninfected. Curiously enough this appears also to be true as regards the finding of bacilli in the wall of the bladder or in the kidney. In one case in particular (205), in which the urine was loaded with pus-cells and organisms, no bacilli and not even round-cell infiltration could be demonstrated deep in the wall of the bladder. Although the urine was foul, the infection had been strictly limited to the most superficial cells. This observation may have important bearing on the caution which should be exercised in translating our deductions from animal studies to man. Physical conditions may be made as nearly analogous as possible, but the differing biochemic reactions remain profoundly difficult of interpretation. This is one reason for regarding our work, even if it were further advanced, as confirmatory rather than conclusive.

TABLE OF RESULTS*

No. Dog	Sex	No. of Ureters Slit†	Insoluble Substance in Bladder	Days after Operation	Young's Test	Urinary Findings	Gross Findings	Microscopic Findings	Remarks
150	M.	⇄	—	163	A few drops solution in left renal pelvis	Negative	Left ureter shade larger than right; no dilatation	Negative	..
156	M.	⇄	—	133	..	Negative	Right ureter dilated	Negative	Killed fighting.
158	F.	⇄	—	134	No solution entered ureters	Negative	Ureters and kidneys normal	Negative	Bladder burst at 10 ft. pressure
160	M.	<	—	126	No solution entered ureters	Negative	Ureters and kidneys normal	Cloudy swelling	..
162	M.	⇄	—	116	Left ureter filled	Negative	Ureters and kidneys normal	Negative	Bladder burst at suture line at 10 ft. pressure
185	M.	<	+	64	No solution entered ureters	Pus-cells; organisms; no casts	Ureters and kidneys normal	Negative	..
200	F.	⇄	+	66	Few drops on right side only	Bacilli; cocci; pus-cells; no casts	No dilatation of ureters	Negative	Gram-negative bacillus, probably colon; three weeks pregnant
205	M.	⇄	+ ..	54	..	Great deal of pus and many organisms; no casts; blood	Kidneys normal; no dilatation of ureters	Cloudy swelling	..
207	F.	⇄	+	36	..	Pus; some organisms; no casts	No dilatation of ureters; bladder inflamed	Cloudy swelling	Gram-negative bacillus, probably colon; cocci
208	M.	>	+	34	..	Some pus-cells; strept. and staph.; no casts	No dilatation of ureters; bladder inflamed	Cloudy swelling	All ureters permeable; no effort at healing seen in any case

---

* Clinical conditions good in all; no bacilli found in tissues of any. † In this column > stands for "right"; < for "left," and ⇄ for "both."

Results of Experiments

Before sacrificing the animals with chloroform they were in some cases subjected to the test devised by Young. The results of this test showed that if the physiologic activity of the ureter were not impaired it was equally difficult to inject the renal pelvis whether the ureterovesical valve had been slit or not.

In a single case only was there ureteral dilatation. This may or may have not been caused by the mechanic pressure of reflux, either in whole or in part. The dilatation occurred as in man, at the cephalad and caudad extremities. Such dilatation is probably not entirely if at all of mechanic origin, a case in point being the well-known difficulty of producing dilatation of the stomach by duodenal obstruction. Dilatation of mechanic origin exists, but it occurs at the point of obstruction rather than at a distance from it. It is probable, therefore, that both biochemic and physiologic factors enter in as causative agents when any organ dilates.

One kidney presented a depressed lesion about 1–5 cm. in length by 1–5 cm. in width. It might have been caused by an infarct due to infection from the bladder, but was probably the scar of an old traumatism.

Action of the Ureterovesical Valve

The more fundamental portion of the problem now awaits discussion. That the ureterovesical valve exerts under certain conditions a check-valve-like action on the contents of the bladder is not to be denied. It is cited in every text-book. So long ago as 1898 Young, in an exhaustive series of experiments both in dogs and in man, demonstrated that this action exists. He injected staining material at a pressure of 11 feet and found that in no case was there reflux into the renal pelvis or ureters. The valve held even in human cadavers, in which the ureters were obviously passive. The correlation of this excellent physical study with the physiologic and pharmacologic studies of more recent years seems to us of great importance.

Maydl's classic experiments have also been rightly accepted as demonstrating the mechanic action of the ureterovesical valve, despite the fact that meatal transplantation has not in general given satisfactory operative results. Indeed, so fixed in the minds of surgeons is the idea that an oblique valvular entrance is necessary for protection when any duct enters a viscus that many ingenious forms of technic have been devised to effect or to preserve it. Notable among these have been the measures of Sullivan and of Coffey, who have elaborated skilful methods with a special view to a preservation of the oblique duodenal entry of the common bile-duct.

Until recently, with few exceptions, all efforts to utilize the septic bowel as a urinary reservoir have signally failed. Has this been because of the destruction of the ureterovesical valve alone? This has been the general opinion in the past. Has not the physiologic element in connection with this problem been overlooked? If it be true that nature has provided an abundant "factor of safety" in combining both physiologic and mechanic factors in protecting against reflux, then it may well be that the failure to make a vicarious bladder out of the bowel has been due to the destruction of the mechanic protection, coupled with such serious impairment of the physiologic defense as entirely to overbalance the "factor of safety." Such physiologic impairment may well be accomplished by the injury to the ureter consequent to its transplantation. Dudley Tait (personal communication) may be quoted as saying that the explanation of the recent occasional success of the ureteral rectal implantation should be attributed to the careful protection of the ureter from traumatism by the modern technic. This has been accomplished by discontinuing the use of a permanent catheter after transplantation and by minimizing the number of stitches taken in the ureter. This is directly in line with the idea that reflux is prevented much more by the ureter itself than by the obliquity of its valve. Tait also holds that the importance of the mechanic action of the valve in preventing reflux has been exaggerated.

This consideration calls to mind the history of the patients in whom a mechanically corresponding valve, that situated at the papilla of Vater, was slit in the transduodenal operation of McBurney for the removal of gall-stones. This operation was done many times and, so far as is known, without grave injury to the patient by reason of reflux of duodenal contents into the common bile-duct, liver, or pancreas. It would appear, therefore, that the destruction of this mechanic safeguard must have placed the work of preventing such reflux on the physiologic function of the duct. This implies that the "factor of safety" regarding the prevention of reflux into the liver as well as into the kidneys is in each case a double one, formed by a combination of a mechanic valve and a physiologic contrivance.

Physiologists and anatomists alike, while universally drawing attention to the fact that the mechanic arrangements for the valve are such as to protect the ureter from the transmission of intervesical pressure, do not state that this is its solitary function nor do they summarize the conditions which would obtain if the valve were destroyed. Here we are on the borderland between surgery and physiology and evidently at a point where the first cannot safely advance except through the help of the second. Have we not, in considering the ureteral valve as the paramount protector of the ureters and kidneys from dangers arising from below, been somewhat biased because of having reasoned from a morphologic point of view alone? Have not the underlying principles of physiology and chemistry been overshadowed and forgotten in the tacit acceptance of this purely morphologic explanation? Indeed, it appears to us that the well-known difficulty of reproducing in animals the analogues of human disease, even though all the evident morphologic and physical conditions be duplicated, should suffice to show us that in the discussion of this as well as of other surgical problems, in considering form alone surgeons have as yet taken only the first primitive step. Were we to attempt to reproduce the ordinary symptoms of human disease in healthy human beings we should without doubt be confronted with the same difficulties that are encountered in making these attempts on animals.

With these considerations in mind, and believing that the existing surgical studies of the ureteral meatus had been based too closely on morphology, since the delicate physiologic regulation both as regards protection from ascending infection, if indeed any such process is possible, and as regards the maintenance of normal glomerulotubular pressure, had all been lost sight of, we made efforts to consider the bearing of these points in our experimental work. We did not expect to answer these questions by any single experimental study, but we hoped to make the subject somewhat clearer and to direct attention to the importance of physiology to applied surgery. We slit the valve in dogs in the belief that the ureter was much more than a mere aqueduct for the conduction of urine, and that the generally recognized check-valve action at the meatus was of contributory rather than of paramount importance. We have been led to believe as a result of these studies that, provided the physiologic and chemic balance of the organism and of the ureter were left intact, the importance of the mechanical action of the valve was correspondingly diminished and that its loss would usually be compensated for by the ureter. These ideas are not original, being simply the natural outcome of an application of modern physiology to the study of surgical problems.

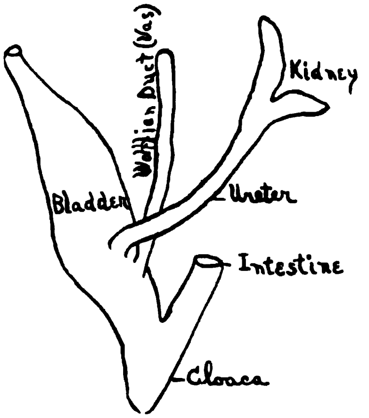


Fig. 162.—Scheme of relations of duct openings. Human embryo, 14 mm. (Huntington, Harvey Lectures). The separation of these openings, which occurs in early fetal life, may account for the so-called ureteral valve.

Cathelin's views as to the valvular function are pointed. In a paper on the mechanism of the ureteral ejaculation, Cathelin says that the meatus does not open after the manner of a sphincter—that there is not the least suggestion of force or contraction. He regards the opening of the valve as purely passive in character, likening it to the opening and closing of the mouth of a fish.

Because of the extreme difficulty of correctly estimating the true functional condition of the kidney by its morphologic appearance after death, it is evident that the final word as to the clinical importance of the ureterovesical valves cannot be written until after a number of dogs having both infected bladders and sectioned valves have been studied over a long period or until death occurs from kidney involvement. Indeed, a control series of dogs which had been similarly infected but in which the valve had not been destroyed would also be necessary.

The present paper deals with the problem as studied through the sixth week of bladder infection only and through the fourth month in the case of uninfected bladders. It is therefore not presented for consideration as a finished statement. If the ureterovesical valve constituted the sum and substance of the "factor of safety" which must enter into the prevention of bladder reflux, the individuals in which the valve had been destroyed and in which there had existed chronic cystitis should, in reasonable time, show some clinical symptoms as well as morphologic changes in the tissue of the kidney. This did not prove to be the case in our experimental series.

Nevertheless, in view of the generally recognized fact that function may be very gravely impaired in organs which show but little or no change under the microscope, we do not wish to be understood as saying that at the time of death the kidneys studied were normal. It is quite certain that they showed no distinct lesion microscopically, and clinically there was no evidence whatsoever of any impairment in health. It is quite possible, however, that at a later date the animals might have developed fatal kidney lesions.

Conclusions

Tentatively we conclude that in experienced hands there is little or no danger in human beings from the operation of meatotomy through the operative cystoscope either as regards immediate hemorrhage or sepsis or as regards late results from injury to the kidney.

The protection from reflux is affected at least as much by physiologic function of the ureter as by the check-valve action at the meatus. These together, rather than the ureterovesical valve alone, constitute the "factor of safety" which prevents reflux.

The ureter alone, almost without exception, sufficed experimentally to prevent reflux even if the uretero-vesical valve had been destroyed. Section of the valve appeared to leave the protective ureteric function intact.

The above data would confirm the opinion expressed by others that renal infections are seldom if ever ascending, but rather hematogenous in origin.

BIBLIOGRAPHY

Beresnegowsky: "Zur Frage über die physiologische Tätigkeit der Ureteren," "Centralbl. f. Physiol.," 1908, vol. xxii, No. 15, p. 461.

Lucas, D. R.: "Studies of the Peristalsis of the Ureter of Dogs by the Graphic Method," "Amer. Jour. Physiol.," 1906, vol. xvii, p. 392.

Lucas, D. R.: "Clinical Aspects of Recent Developments in the Physiology and Pharmacology of the Ureter," "New York Med. Jour.," August 10, 1907, p. 254.

Lucas, D. R.: "Physiological and Pharmacological Studies of the Ureter," "Amer. Jour. Physiol.," 1908, vol. xxii, p. 245.

Young, H. H.: "Hydraulic Pressure in Genito-urinary Practice, Especially in Contracture of the Bladder," "Johns Hopkins Hosp. Bull.," May, 1898, p. 100.

Kropeit: "Uretersteine," "Deutsche med. Wochenschr.," 1911, No. 22, p. 1053.

Schmidt: "Ueber Ureterplastik," "Centralbl. f. Chir.," 1912, No. 1.

Pietkerwicz: "Zwei Fälle von cystischer Erweiterung der vesikalen Ureterenden," "Zeitschr. f. Gyn. u. Urol.," 1911, vol. ii, p. 261.

Cathelin: "Sur le mécanisme de l'éjaculation urétéral," "Ann. d. mal. d. org. genito-urin.," 1909, vol. i, pp. 251–263.

Schewkunenko: "Portio intramuralis der Ureteren und Trigonum Vesicæ," "Zeitschr. f. Urol.," 1911, vol. v, No. 10, p. 851.

Piersol: "Human Anatomy," p. 1900.

Decker und Gagstatter: "Klinik und Therapie der Steine im Beckenteile des Ureters," "Wien. klin. Wochenschr.," 1911, No. 8.

Pappa: "Contribution à l'étude des calculs de l'uretèri," "Thèse de Paris," 1908.

Pasteau: "La dilatation intra-vesicale de l'extrémité inférieure de l'uretère," "Assn. Française d'Urologie," 1904.

Picqué: "Trois gros calculs enclavés à l'extrémité inférieure de l'uretère droit, etc.," "Bull. Soc. de chir. de Paris," 1905, p. 31.

Albarran: "Prolapsus intra-vesical de l'uretèri," "Assn. Française d'Urologie," 1904.

Thompson: "Impaction of Calculus at the Vesical End of Each Ureter," "Edinburgh Med. Jour.," April, 1911.

Huntington: "The Genetic Interpretation and Surgical Significance of Some Variations of the Genito-urinary Tract," "Harvey Lectures," 1906–7, p. 222.

A NEGLECTED PRINCIPLE IN CYSTOSCOPY *

W. F. BRAASCH

In a recent admirable article on the genesis of the modern cystoscope[1] we find but scant mention made of the direct cystoscope. Following the lead of European observers, the majority of American urologists today are employing the lens type of cystoscope. In the choice of such an instrument one may well be bewildered by the array to be found in the various catalogues. They vary from the simple indirect lens of Nitze[2] to the complete and all-embracing cystoscope of recent invention. It is, therefore, with much hesitation that the writer ventures to describe another cystoscope and add to the already unlimited armamentarium. Again, it is not so much to the instrument that he wishes to draw attention as it is to the employment of the somewhat neglected if not new method of direct cystoscopy.

The direct cystoscope has been variously employed in the cystoscopic past. Foremost among the list of adherents to the direct method we find the name of Howard Kelly.[3] His well-known methods need no further description, and today they are still widely employed. His method has not, however, received universal acceptance for several reasons, namely: (1) The preponderance of lens sentiment; (2) the awkward position and exposure of the patient, particularly if an anesthetic be given; (3) the inability to employ the method in the male. The credit for presenting the first direct cystoscope of the modern type should be given to Bransford Lewis.[4] His instrument permitted the dorsal position in the male, and included catheterizing tubes. Instead of relying on atmospheric pressure to distend the bladder,

---

* Reprinted from the "Amer. Jour. of Urol.," March, 1912, pp. 115–119.

as in the Kelly method, he employed an air-pump with a retaining window. Direct air cystoscopes, similar to that of Bransford Lewis, appeared in rapid succession, Koch, Belfield, Snell, Elsner,[5] Luys,[6] etc. These instruments did not receive wide-spread employment largely because of the awkwardness and pain caused by air distention so employed, and by the general recognition that water was the better bladder medium in cystoscopy. The employment of water in this type of air cystoscope is responsible for its survival, and to my predecessor, the late M. C. Millet, must be given credit for first demonstrating the value of this method. He was among the first to employ the direct view air cystoscope, and, after finding the use of air so often unsatisfactory, substituted water for air. The use of water in the direct cystoscope embodied an entirely new principle. At first thought the idea of looking through a tube of water hardly seems practical. The water medium magnifies the field slightly and brings it out in clear relief, but does not distort the object observed. Furthermore, it is less painful than air in the bladder, and is more easily controlled. Having briefly outlined the origin of the method employed in the Mayo Clinic, I will discuss the comparative advantages of the lens instruments now used and the direct view water cystoscope.

The lens instrument offers the following advantages: (1) It gives a field of greater circumference; (2) it permits a clearer view of the anterior wall of the bladder in the male; (3) it offers a more detailed and magnified view of the bladder mucosa.

While it is true that the field of vision in an observation lens is greater than through a direct cystoscope, nevertheless with many catheterizing lenses the actual diameter of the field is not very much larger. Moreover, what one loses in circumference of the field is at least partially made up by the increase in perspective gained by direct inspection. Although the anterior bladder-wall is easily viewed through an observation lens, still in the female it can be inspected quite as easily through the direct cystoscope. By partially emptying the bladder and by permitting the roof to sag down, but little escapes inspection in the male bladder. With greatly hypertrophied prostates it may occasionally become difficult to inspect the anterior wall of the bladder. While the detailed and magnified view of the bladder mucosa and ureteral meati obtained through a lens may occasionally be of some advantage, nevertheless the picture obtained by the unaided eye is a truer one and loses no data of practical value.

The Advantages of the Direct View

(1) Its simpler mechanism. (2) A clearer view of the field in case of hemorrhage. (3) The field is natural, requiring no interpretation. (4) Use as urethroscope as well.

The simpler mechanism of the direct cystoscope offers the following advantages: (*a*) It is less often damaged and in need of repair than the fine lens adjustments; (*b*) it is more easily sterilized by momentary immersion in pure phenol, followed by washing in water; (*c*) its use does not require careful preliminary irrigation of the bladder. With a freely bleeding bladder mucosa it is frequently impossible to obtain a clear view through a lens cystoscope in spite of continuous irrigation. With the direct instrument, on the other hand, we are looking through a clear stream of water which is continuously entering the bladder and washing the observed area, and bleeding is seldom so great as to render examination impossible. Most beginners in the use of the lens cystoscope complain of the difficulty in interpreting the field observed. Although the inversion of the object is now corrected by the latest lenses and the interpretation is somewhat simplified, nevertheless the magnification in the frequently blurred field is confusing to the novice. On the other hand, the direct natural view is readily and accurately interpreted in a comparatively short time.

The direct cystoscope may also be employed as a urethroscope. Although water is now generally recognized as the best medium adapted to view the posterior urethra, it is only recently that it had been adapted to the use of the lens urethroscope. We have examined the posterior urethra through direct inspection with water distention for a number of years. While the view thus obtained may lack the magnified detail afforded by the lens instruments, the actual value of which is questionable, everything of practical importance is clearly visible. Although the importance of routine urethral examination has undoubtedly been recently exaggerated, an instrument which will permit urethroscopic as well as cystoscopic examination is frequently of considerable value. Of particular interest is the direct inspection of the prostate from the viewpoint of the prostatic urethra from which the relative size, position, and frequently character of the enlargement is readily ascertained.

Method of Using the Direct Cystoscope

The instrument (Fig. 103) is sterilized by momentary immersion in phenol and then washed in sterile water. No previous irrigation of the patient's bladder is necessary. After introducing

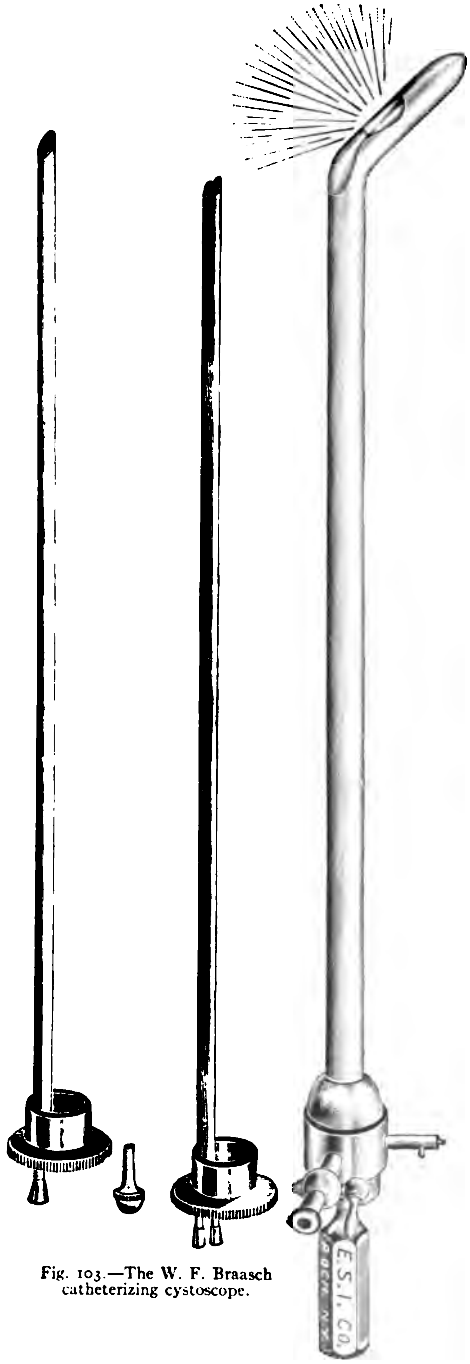


Fig. 103.—The W. F. Braasch catheterizing cystoscope.

the cystoscope the water stop-cock is connected with a receptacle containing boric-acid solution, which we use to distend the bladder. Care must be taken to remove all bubbles of air from the cystoscope, otherwise the vision will be interfered with. This is easily done by removing the inspection window and readjusting when the tube is filled with water or by merely raising the beak and turning the distending medium off and on. The trigone and lower two-thirds of the bladder will be easily inspected without moving the instrument much. In order to view the roof and anterior wall the patient's pelvis may be elevated, the bladder fluid allowed to escape partially, and, with the beak pointing toward the floor of the bladder, the sagging roof is readily brought into view. The urethra is likewise easily inspected by merely withdrawing the instrument into the urethra under constant water-pressure. If after inspecting the bladder ureteral catheterization is indicated, we have the choice of several catheterizing tubes: A bilateral tube for catheters size ch. 6; a single tube for size ch. 7; and a single tube for size ch. 9. The catheterizing tubes are removable and may be sterilized by boiling. Wax-tipped catheters may be used by introducing the catheter reversed into the single tubes, leaving the wax tip protruding. The tubes are straight, so that the slightest ureteral obstruction and often its character are readily felt by the catheter. The cystoscope permits only of direct catheterization, and, in our experience, this has always sufficed with any ureter which could possibly be catheterized. Probably the greatest value of the direct cystoscope is its simplicity, which must commend the instrument to any observer and particularly to the beginner.

REFERENCES

1. Lewis, B.: "Amer. Jour. Urol.," 1909, vol. v, pp. 144–161.
2. Nitze: "Cent. f. d. Krankh. der Harn- und Sex.-Org.," 1897, Hft. 7, p. 369.
3. Kelly: "Bull. Johns Hopkins Hosp.," December, 1893.
4. Lewis, B.: "Jour. Cutan. and Genito-urinary Dis.," 1900, p. 420.
5. Elsner: Pilcher's "Practical Cystoscopy," pp. 82, 83.
6. Luys: "Assoc. franc. d'urol. Proc.-verb," 1905, pp. 467–482.

RESULTS IN THE TREATMENT OF TUMORS OF THE URINARY BLADDER *

E. S. JUDD

The surgical treatment of tumors of the bladder is surrounded by a host of difficulties. Chief among these are to be mentioned, first, the importance of preserving the anatomic relationship; second, the complications arising from the multiplicity of tumor types, and third, the inaccessibility of the lesion.

The anatomic relationship must be preserved in order to maintain function. It is necessary to preserve the orifice into the bladder for the ureters and, if one or both of them be destroyed, one or both must be transplanted so as to enter the bladder at some other point. It is also necessary to maintain the normal outlet with its muscular mechanism and power of urinary control.

While most tumors of the bladder are papillomas, they occur frequently in multiple form. Usually there are one large and several small tumors. The large tumor is apt to overshadow the smaller tumors, one of which may easily escape notice. Recurrence of papillomas is seldom local, but is often seen in a different quadrant of the viscus. Cells brushed off in removing the tumor are prone to engraft themselves on any tissue with which they come in contact. Recurrence as a fringe about the orifice of the urethra is also common, and this is probably explained by cells which have been left free in the bladder and which were forced against the mucous membrane at this point by the contractions of the organ. Too much emphasis cannot be laid on the importance

---

*Read in the Symposium on Treatment of Tumors of the Bladder in the Section on Genito-urinary Diseases of the American Medical Association, at the Sixty-third Annual Session, held at Atlantic City, June, 1912. Reprinted from "Jour. Amer. Med. Assoc.," November 16, 1912, vol. lix, pp. 1788–1791.

of a careful search of the entire floor of the bladder for minute papillomas after the large tumor has been removed, and of the importance of the complete removal of all cells adjacent to the large and small areas of neoplasms.

A large percentage of the tumors of the bladder occur in the base or on the wall close to the base, at or near one of the openings of the ureters or of the urethra. These positions render the lesions extremely inaccessible to the surgeon, and make their treatment most difficult with a high percentage of recurrences.

Up to the present we have examined in our clinic 114 cases of primary tumors of the bladder. Eighty-four were in males and 30 in females. One patient was under ten years of age and one over eighty. The greater number were between the ages of forty and seventy; the average age was 53.1 years.

We have classified these tumors, according to the clinical course, into benign and malignant. In the group of benign cases are included fibromas and myomas. Only 2 of the 114 cases in our series belonged distinctly to this group, and these were fibromyomas. In the group of malignant cases we have included papillomas and carcinomas.

Estimated from a clinical point of view, all papillomas are malignant, though one type of papillary tumor may be histologically malignant at the onset, while another type may early show no evidence of invasion of the surrounding tissues. All types of papilloma have the power to recur and also to destroy life, in the same manner as the recognized malignant tumors. In all probability if the patient lived long enough all papillomas would become histologically malignant.

In 22 of our cases more than one-half of the bladder was involved, and in 4 it was completely filled with the tumor.

METHODS OF TREATMENT

The method of operative procedure and treatment must be determined: (1) By the general condition of the patient; (2) by the cystoscopic findings. Arteriosclerosis, renal insufficiency, myocarditis, etc., are factors contraindicating radical procedures.

Bimanual examination by vagina in the female and by rectum in the male is most important in the diagnosis, as thus we may be able to determine the presence and extent of induration. Many times cases will be eliminated in which otherwise operation might be attempted.

The cystoscopic examination is most important not only in determining the number, location, and extent of the lesions, but also in helping to differentiate a bleeding hypertrophied granulating surface from a true neoplasm. This benign granulating surface is often seen in prostatic hypertrophy, cystitis, and particularly in tuberculosis. It is also present in cases in which tumors and inflammatory masses are pressing into the bladder from the outside. A stone in the lowest point of the ureter will sometimes force the mucous membrane at the meatus out into the bladder, thus giving the appearance of a tumor. An *x*-ray picture will usually differentiate this condition.

When possible, it has been our custom to excise, through the cystoscope, a specimen of the growth large enough for a microscopic examination. This procedure is valuable in differentiating cases of benign hypertrophies and inflammations of the mucous membrane from the vesical tumors.

If there be palpable metastases or considerable induration in the base of the bladder, the case should be considered inoperable. If there be no induration, but a bladder apparently completely filled by the tumor, the case may still be operable, since the pedicle of the large tumor may involve but a small part of the mucosa of the bladder.

Lymphatic involvement and visceral metastases occur but rarely.

One of the chief advantages in the transperitoneal operation is that it affords an opportunity to observe the pelvic lymph-nodes and the abdominal viscera. In two cases, because of glandular involvement (one because of extension to the peritoneum and omentum), and in one case because of metastatic nodules in the liver, we have been deterred from removing otherwise operable tumors of the bladder.

The prostate is rarely involved except in the late stages. Should there be any question regarding such involvement, however, the gland should be removed with the tumor. In five of our cases a prostatectomy was necessary.

TABLE 1.—GROUP 1: PATIENTS WITH COMPLETE DATA, NOT OPERATED ON

No.	Age	Sex	Duration Symptoms When First Seen, Months	From Beginning Symptoms to Death, Months
1	62	M	16	17
2	83	M	180	181
3	61	M	12	17
4	66	M	24	27
5	64	M	8	11
6	58	M	12	13
7	73	M	24	25
8	61	M	8	21½
9	41	M	3	16
10	44	M	2	2½
11	58	M	60	66
12	72	M	24	26
13	50	F	9	25½
14	65	M	18	19½
15	38	M	5	6
16	75	M	4	6
17	69	F	72	76
18	49	M	½	1
19	54	M	3½	7½
20	58	M	12	18
21	58	M	10	13
22	70	M	30	33
23	7½	F	84	84

Summary: Males, 20; females, 3.
Average duration of life from beginning symptoms to death (23 patients), thirty months.

RESULTS OF TREATMENT

In order that the results of treatment may be studied to the best advantage, the 114 cases have been divided into three groups: The first group includes all cases in which no operation was done—(*a*) Because of the extent and location of the tumor; (*b*) because of the poor general condition of the patient; or (*c*) because the patient did not remain for treatment. Thirty-eight of the 114 cases are in the first group—30 males and 8 females. Counting all the cases of this group which we have been able to follow (23 : 20 males, 3 females), we found that the average duration of life from the beginning of any symptoms was thirty months. One patient lived one month and another two and one-half months from the beginning of symptoms and then died apparently of the disease. This would indicate that the trouble had existed for some time before any symptoms appeared. On the other hand, we have had one inoperable case in which the patient lived one hundred and eighty-one months (fifteen years) from the beginning of symptoms. Here the early symptoms may have been due to some process other than the neoplasm. If these two cases of short duration and the one of long duration be omitted in estimating the remaining cases, the average duration of life from the beginning of symptoms to the time of death is twenty-six months.

The second group (30 cases: 19 males and 11 females) includes all cases in which a transperitoneal operation was done. This type of operation was chosen because the neoplasm was malignant and on a sessile base, which made it necessary thus to resect the entire thickness of the wall of the bladder. In 9 of the 30 cases it was necessary, because of the site of the lesion, to transplant one ureter into another quadrant of the bladder. The prostate was involved and removed in two of the cases. Three of the 30 patients died in the hospital. The findings in these 3 cases were as follows:

Case 1.—Man aged sixty-two years. Left quadrant of bladder removed and ureter transplanted. Pathologic diagnosis, carcinoma. Patient died on seventh day. Autopsy showed acute nephritis in right kidney, with chronic hydronephrosis and functionless kidney on left side.

Case 2.—Man aged sixty-five years. Carcinoma involving considerable of base removed. Left ureter transplanted. Impossible to close base of bladder. Patient died on seventh day. Autopsy showed extravasation and infection extending behind the peritoneum on both sides. No infection in peritoneum.

Case 3.—Man aged forty-nine years, alcoholic, bad risk. Carcinoma involving base between ureters. Patient died on the third day. Autopsy showed general intestinal paresis, fatty degeneration of liver, and chronic nephritis. No infection.

TABLE 2.—GROUP 2: TRANSPERITONEAL OPERATIONS

No.	Age	Sex	Duration Symptoms When First Seen, Months	From Operation to Death, Months	From Operation to Last Heard From, Months	From Beginning Symptoms to Death, Months	From Beginning Symptoms to Last Heard From, Months	Condition When Last Heard From
1	39	F	24	..	60	..	84	O. K.
2	50	M	14	..	59	..	73	O. K.
3	49	M	1	36	..	37	..	Dead.
4	22	M	11	..	54	..	65	O. K.
5	54	M	24	47	..	71	..	Dead.
6	62	M	12	44	..	52	..	Dead.
7	45	M	12	23½	..	35½	..	Dead.
8	37	F	24	..	48	..	72	Recurrence.
9	61	F	10	2	..	12	..	Dead.
10	17	F	60	21	..	71	..	Dead; int. condition
11	70	M	4	13	..	17	..	Dead.
12	29	F	2	..	43	..	45	O. K.
13	58	M	36	..	39	..	75	O. K.
14	62	M	60	7*	..	60	..	Dead.
15	56	M	2	17	..	19	..	Dead.
16	54	M	12	..	35	..	47	O. K.
17	35	F	5	(No other data)	..	..	..	..
18	50	M	12	..	28	..	40	O. K.
19	34	F	36	..	26	..	62	O. K.
20	51	M	3	2	..	5	..	Dead.
21	46	M	24	..	33	..	57	O. K.
22	49	M	6	..	16	..	22	O. K.
23	50	F	48	..	8	..	56	O. K.
24	52	M	32	..	15	..	47	Recurrence.
25	44	F	24	..	15	..	39	Probable recurrence.
26	57	M	14	..	13	..	27	Probable recurrence.
27	65	M	1	5*	..	1	..	Dead.
28	45	F	4	..	7	..	11	O. K.
29	31	F	16	..	3	..	19	O. K.
30	49	M	24	2*	..	24	..	Dead.

*Days.

Summary:

Males, 19; females, 11.
Average duration of symptoms when first seen 8.5 months.
Average duration of life from beginning of symptoms to death or until last heard from 41.5 months.
Patients who have lived five years 3
Patients who have lived three years 10
Operative mortality .... 10 per cent.

TABLE 3.—GROUP 3: SUPRAPUBIC OPERATIONS

No.	Age	Sex	Duration Symptoms When First Seen, Months	From Operation to Death, Months	From Operation to Last Heard From, Months	From Beginning Symptoms to Death, Months	From Beginning Symptoms to Last Heard From, Months	Condition When Last Heard From
1	20	F	24	12	..	36	..	Dead.
2	29	M	12	50	..	62	..	Dead.
3	69	M	54	41	..	95	..	Dead.
4	43	M	48	..	70	..	118	O. K.
5	56	M	24	..	72	..	96	O. K.
6	43	F	12	..	72	..	84	O. K.
7	37	F	12	63½	..	75½	..	Dead.
8	69	M	12	..	32	..	44	O. K.
9	54	M	12	..	70	..	82	O. K.
10	42	M	24	15	..	39	..	Dead.
11	57	M	144	31	..	175	..	Dead.
12	27	M	15	(No other data)	..	..	..	..
13	41	F	24	24	..	48	..	Dead.
14	60	M	8	..	37	..	45	O. K.
15	33	M	36	..	36	..	72	O. K.
16	66	M	36	3	..	39	..	Dead.
17	69	M	12	..	31	..	43	O. K.
18	69	M	12	..	2	..	14	O. K.
19	72	F	24	2	..	26	..	Dead.
20	66	M	18	8½	..	26½	..	Dead, pneumonia.
21	62	M	12	19	..	31	..	Dead.
22	60	M	24	1	..	25	..	Dead.
23	38	F	12	10	..	22	..	Dead.
24	47	M	24	..	6	..	30	Recurrence.
25	71	M	24	..	5	..	29	O. K.
26	50	M	36	..	4	..	40	O. K.
27	70	M	3	¾	..	4	..	Dead.
28	61	M	1	(No other data)	..	..	..	..
29	60	M	12	..	1	..	13	O. K.
30	63	M	24	..	1	..	25	O. K.
31	44	M	42	..	¼	..	42	O. K.
32	59	M	5	..	33	..	38	O. K.
33	47	M	24	(No other data)	..	..	..	..

Summary:

Males, 27; females, 6.		
Average duration symptoms when first seen . . .	24.4	months.
Average duration of life from beginning of symptoms to death or until last heard from	46	months.
Patients who have lived six years	4	
Patients who have lived three years	8	
Operative mortality	3	per cent.

Of the remaining 27 patients, 9 are reported dead and 17 living. One has not been heard from. Three patients have lived five years and are free from symptoms at present. Ten have lived three years, though one probably has recurrence at this time. Of the 17 patients living at this time, 4 have been operated on for recurrences. Two had secondary transperitoneal operations, one suprapubic, and one was treated with the high-frequency current. In one case, because of involvement of the wall of the bladder in the region of the sphincter muscle, the entire bladder was removed and the ureters were transferred to the loins. This patient has lived two and one-half years and is comfortable, with no evidence of recurrence at present. One of the ureters ceased to drain at the end of the first year.

The average duration of symptoms in the patients on whom the transperitoneal operation was performed was 18.5 months. The average duration of life since the operation is 24.4 months, and the average duration of life from the beginning of symptoms up to death or to the present time is 41.5 months. Figuring the duration of life without operation to be twenty-six months, we find that these patients have gained an average increase of life of 15.5 months each.

The third group includes the cases in which a suprapubic operation was done without opening the peritoneum. This operation was performed in 33 of the cases (27 males and 6 females), and was chosen because the tumor was on a pedicle and not infiltrating into the wall of the bladder or because the patient's general condition would not warrant a more radical procedure. One patient, a man aged seventy-three, died at the end of three weeks. The autopsy showed marked general arteriosclerosis and nephritis, with no evidence of healing in the bladder.

In this series the prostate was removed with the tumor in 3 cases. The average duration of life from the beginning of symptoms to time of death, or to the present in these suprapubic cases, is forty-six months. This indicates that these patients have gained the difference between forty-six months and twenty-six months (the average duration of life without treatment), or twenty months, by having the operation performed. The greater duration of life in this series than in the transperitoneal series is probably due to the fact that the transperitoneal series is composed of the cases of indurated, infiltrating tumors, while the suprapubic were mostly those of pedunculated tumors which were either benign or early malignant neoplasms.

Four patients operated on suprapubically are living without any evidence of recurrence more than six years after the operation. Eight are free from symptoms three years after operation. Three of the 33 patients have returned and have been treated for recurrence.

The technical points in the various types of operations for tumors of the urinary bladder have changed very little in the past few years. We believe that in these operations, as well as in operating on any other malignant tumor, the tumor should either be excised with the cautery, or the cut edges remaining after the tumor has been removed should be thoroughly cauterized. This is especially important in all papillomas.

The employment of the high-frequency current is one of the most useful adjuncts in the treatment of these tumors. We have used this method of treatment in 17 cases. This number includes 11 cases of recurrence after previous operations done in our clinic and elsewhere. The patient longest under observation since treatment by the high-frequency current was seen after fifteen months. In this case there is no evidence of a return. Five patients have been examined one year after treatment and in none was there any sign of recurrence. No original non-papillomatous growths have been treated by this method, though in several instances recurrences of these tumors have been treated with considerable satisfaction, at least in relieving symptoms. We have found the villous growths on small pedicles the most favorable type for treatment by the high-frequency current.

Knowing the great tendency to recurrence and the possibility of considerable progress in the growth before the appearance of symptoms, it has been our custom to examine these cases by the aid of the cystoscope every three to six months after operation for at least two years. In this way recurrences are discovered and treated early with the high-frequency current. While the results in our cases are not so encouraging as we would like, they are not altogether discouraging. We believe that if patients can be seen a little earlier and technic can be improved so that a more radical excision may be done with a greater degree of safety, the results in the treatment of tumors of the bladder may be made to compare favorably with the results in the treatment of malignancy in other organs.

TUMORS OF THE URINARY BLADDER *

A STUDY OF 114 CASES

E. S. JUDD

It is my purpose to present a general review of the subject of tumors occurring in the urinary bladder, basing the study on data obtained from 114 cases which were observed in Mayo Clinic, St. Mary's Hospital.

According to Guret and Küster, tumors of the bladder form 0.39 to 0.76 per cent. of all tumors occurring in the human body.

With regard to the occurrence of this malady in the sexes, males are affected about three times as often as females; 84 of our 114 cases were in males and 30 were in females.

Tumors of the bladder may be observed in all periods of life, though the condition is most frequently seen between the ages of forty and seventy years. Tumors rarely occur in this region during childhood, though when they do occur they are usually of the connective-tissue variety, *e.g.*, sarcomas. In all of our series we have not seen a single sarcoma; however, we have observed only one patient under ten years of age. This was a case of angioma presenting into the bladder and rectum.

TABLE I

Patients under 10 years	1
Patients 10 to 20 years	3
Patients 20 to 30 years	5
Patients 30 to 40 years	11
Patients 40 to 50 years	16
Patients 50 to 60 years	35
Patients 60 to 70 years	30
Patients 70 to 80 years	12
Patients 80 to 90 years	1
	114
Age of youngest with carcinoma	17
Age of oldest with carcinoma	83
Average age	53.1 yrs.

---

*Read in the Section on Surgery of the Arkansas Medical Society, at the Thirty-sixth Annual Session, held at Hot Springs, May, 1912. Reprinted from the "Jour. Arkansas Med. Soc.," August, 1912.

Only three of the 114 cases were classified as distinctly benign. The remaining 111 were either papillomas or carcinomas. Of the benign cases, with the exception of the case of angioma, there were two fibromyomas, one occurring at fifty years of age and the other at sixty-one years.

Etiology.—Our knowledge of the etiology of tumors of the bladder does not differ from our knowledge of the etiology of tumors in other regions. In some cases chronic irritation is undoubtedly a factor in producing a hyperplasia of the mucous membrane, and this may later become a neoplasm. In two of our cases in which a stone was found, the history indicated that it had preceded the tumor. The irritation from the stone might have been a causative factor in these two cases.

True stone formation was seen in but a small percentage of these cases, though most of the advanced cases had incrustations and deposits of salts on the surface of the tumor, which were clearly secondary to the formation and not an etiologic factor in the causation of the tumor. Some authorities attribute the origin of vesical tumors to parasitic causes, and, although nothing definite has been proved, it is at least interesting to note reports such as Ferguson's (Egypt), who found that in 40 cases of primary malignancy of the bladder all had the bilharzia infection at the same time. The fact that individuals employed in anilin factories are especially prone to tumors of the bladder has been known for some time, and this is taken as a factor in support of the theory of irritation. Chronic cystitis is a symptom which usually develops after the growth is well advanced: it seldom precedes the growth.

Anatomic Findings.—The 114 cases in this report relate to those of primary vesical neoplasms and do not include tumors of the prostate or of any of the abdominal viscera which frequently invade the bladder from the outside.

Vesical tumors may be classified, according to the clinical course, into benign and malignant. The benign cases include the adenofibroma and myoma. These cases are exceptionally rare; in the 114 cases we observed but two distinctly of this class. They were fibromyomas. The malignant cases include carcinoma, sarcoma, and myxoma. One hundred and eleven of our 114 cases were carcinomas or papillomas. The papilloma, which is by far the most common type of tumor of the urinary bladder, should be put into a class by itself. There has been considerable discussion regarding its malignancy, and most observers now recognize a benign and malignant type and distinguish the malignant by the breaking through of the epithelial elements into the blood and lymph-spaces or into the connective tissue.

Estimated from a clinical aspect, all papillomas are malignant and run the same course. They have the power to recur and also to destroy life in the same manner as do recognized malignant tumors. In all probability all papillomas would become malignant histologically if the patient lived long enough. Some papillomas are definitely malignant at the onset. In these there is a marked breaking through of the epithelial elements and a round-cell infiltration about the base. It is undoubtedly true that there is a transition from the so-called benign to the malignant type, and that we have in the simple papilloma at least a precancerous condition. The papilloma varies in size from a small, fine fringe to a tumor which fills the bladder. The neoplasms occur in at least 50 per cent. of the cases—usually one large tumor and a number of small ones.

In 22 of our cases more than one-half of the wall of the bladder was involved, and in 4 the bladder was completely filled by the growth.

In the great majority of cases the papillary tumors are situated on the basal portion of the bladder near one or the other of the ureters or at the urethral opening, which can be almost obscured by the villous tumor placed over it. They are more rarely on the lateral walls and only exceptionally in the dome.

Flattened epithelial cancer or epitheliomas occurred 17 times in 114 cases. We did not find a case of adenoma, sarcoma, or dermoid in the entire series.

Two cases of fibromyomas were examined in one week, and are the only cases of this type which have been observed in our clinic. I mention this to show the comparative rarity of these benign tumors.

Symptoms.—In 112 of the series the average duration of symptoms before the individual came for treatment was 36.59 months. Fourteen patients gave a history of symptoms over five years, and if these be omitted, the average duration for the remaining 98 (2 cases unknown duration) would be 21.14 months each. This would indicate that the patients had suffered for a long time before seeking relief, but it is not surprising when we consider the manner in which the symptoms occurred and the interval of complete relief between attacks.

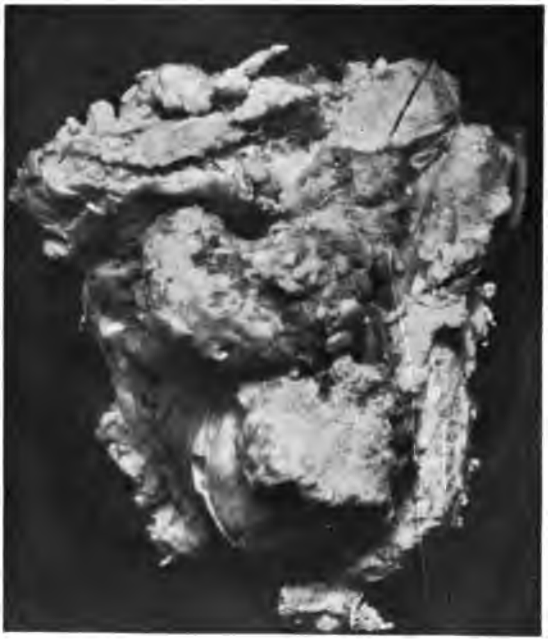


Fig. 104.—Case No. 33449. Showing entire bladder (removed at operation) open. Two large carcinomatous masses in center.

Bloody urine is a characteristic symptom. It nearly always occurs as a hemorrhage in the beginning, but soon subsides, leaving the individual apparently as well as before. There may be no recurrence of the hemorrhage for months or years, and during the interval there will be no microscopic evidence of blood. However, the bleeding will surely return and the intervals between will become less until the hemorrhage is continuous. Continuous hemorrhage invariably means malignancy. The sudden sharp hemorrhage which gradually clears away should always be suggestive of a tumor, especially if it be revived by local applications or the passing of sounds. Fragments of the tumor may be passed. If the tumor be situated so that it does not interfere with empty-

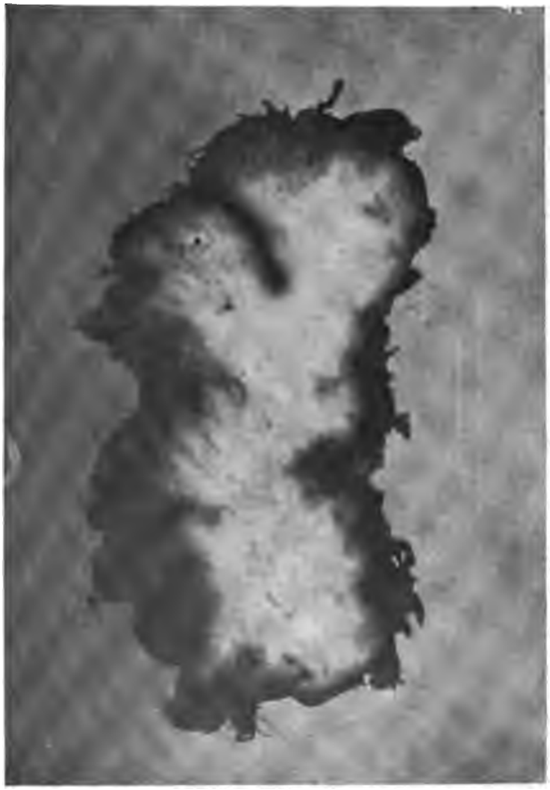


Fig. 105.—Case No. 43956. Section through carcinomatous bladder. White center composed of a very cellular growth. Edges made up of short, filiform, papillary outgrowths.

ing the bladder, there may be no interference with urination after the blood has all passed. Cystitis usually develops between two to three years after the beginning of the symptoms, and from this time the frequency and pain gradually increase.

Hemorrhage is usually estimated to be the first symptom in 85 per cent. of the cases. In this series bleeding occurred first in 69 cases (47.9 per cent.).

TABLE II.—FIRST SYMPTOMS

Bleeding	69
Frequency	57
Pain before and after micturition	26
Burning	24
Hesitancy or difficulty	14
Pus in urine	2
Dribbling	1
No urinary symptoms	1
Tenesmus	1
Retention	2
Bloody diarrhea	1
Growth of exstrophy	1
Lump groin	1
Mass abdomen	1
Pain not accompanying micturition:	
Bearing down	1
Back	2
Lower down	2
Hypochondrium	1
When defecating	1
In penis	1

Bleeding followed by pain and difficulty was the first symptom in the three benign cases.

TABLE III.—PAIN

Pain of some nature	88
No pain	26
Before micturition	4
During micturition	27
At end of micturition	7
After micturition	2

Pain was also present, not connected directly with micturition, in the bladder and lower abdomen, and radiated into the back and lower limbs, especially in advanced malignancy.

Frequency from every few minutes to 2 times at night was noted in 92 cases.

Blood.—Blood varied from slightly tinged urine or a single drop at end of urination to large amount of bright red blood and clots present in 93 cases. No blood in 10 cases.

Forty-two patients had lost in weight. One patient gained; no change in 4.

Practically every specimen of urine showed upon repeated examinations albumen, blood, or red blood-cells and pus. The reaction was inconstant, varying in the daily specimens from the same patient. Specific gravity was also inconstant and varied in the same way.

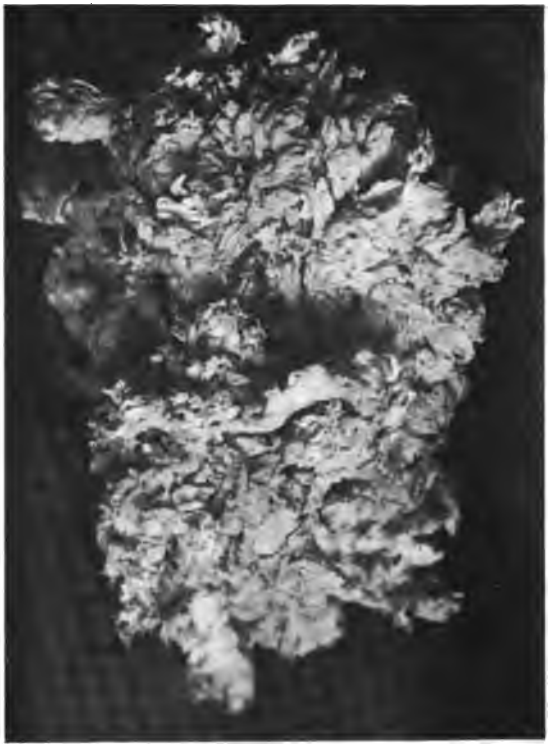


Fig. 106.—Case No. 34232. Malignant papilloma of bladder.

The prostate was enlarged in 32 of the cases and in 2 was involved secondary to the bladder involvement.

Diagnosis.—In many instances the diagnosis of these tumors can be established almost to a certainty from the history. Many times a fragment of the tumor large enough for a microscopic examination is passed, and by sectioning this the positive diagnosis is made.

The cystoscope has come into such common use and can be manipulated so safely that patients even with a slight indication of this sort of trouble should not be denied a cystoscopic examination. By this method of examination the source of the hemorrhage, the amount of accompanying cystitis, the exact position, size, and number of tumors can be determined, and in nearly every case enough of the tumor can be excised through the cystoscope for microscopic diagnosis.

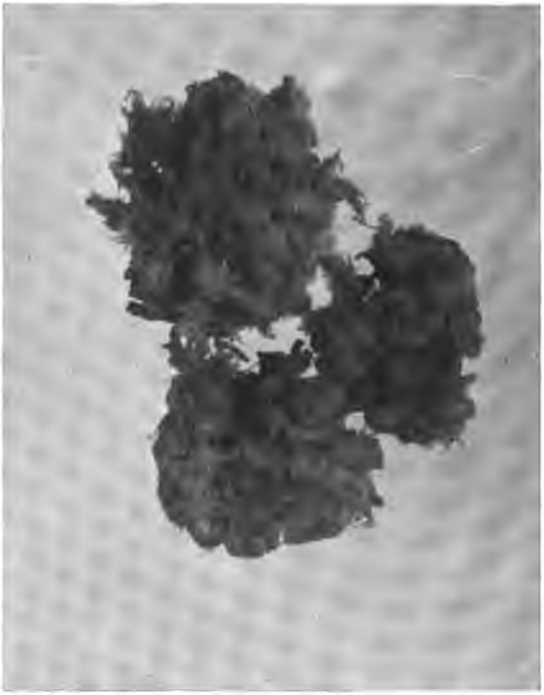


Fig. 107.—Case No. 29831. Multiple papillomas of bladder with long, thin projections.

Prognosis.—The prognosis is always grave. Thirty-seven of our series of 114 patients were inoperable when examined, because of the extensive involvement by the tumors. Many others were in poor condition because of infection which extended through the entire tract, as well as because of the loss of a great amount of blood. Fortunately, the extension into the lymphatics is very slow, and metastatic foci are seldom seen.

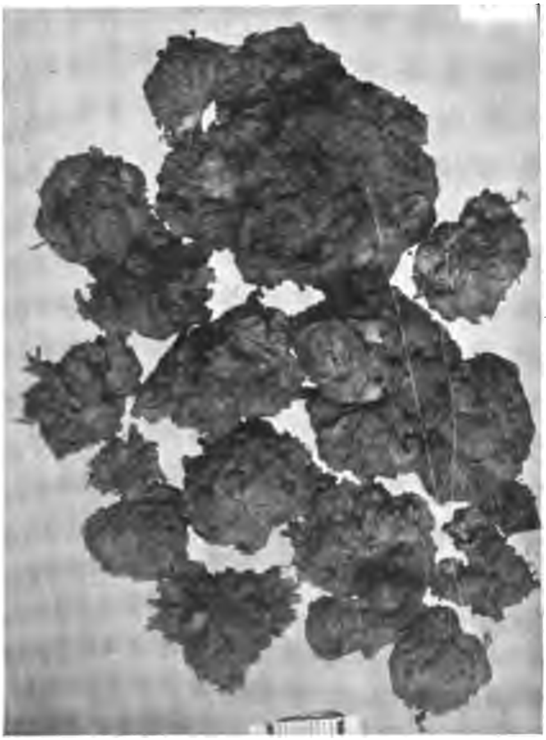


Fig. 108.—Case No. 44996. Multiple malignant papillomas of bladder—bulb-like in appearance.

Recurrence in the bladder is very common, especially the papillary type of tumor. It is quite probable that many of the so-called recurrences are not recurrences, but lesions which were developing when the larger tumor was removed, but were too small to be seen. The recurring lesion seldom springs from the site of the primary growth. The recurrence may appear at any point in the bladder, though it will most often be seen as a fringe about the urethral orifice. In two of our advanced cases the growth was grafted into the incision in the abdominal wall and a large tumor sprang up in the scar. Recurrences at the outlet of the bladder probably occur from the grafting of cells that were brushed off in removing the tumor and were dropped into the

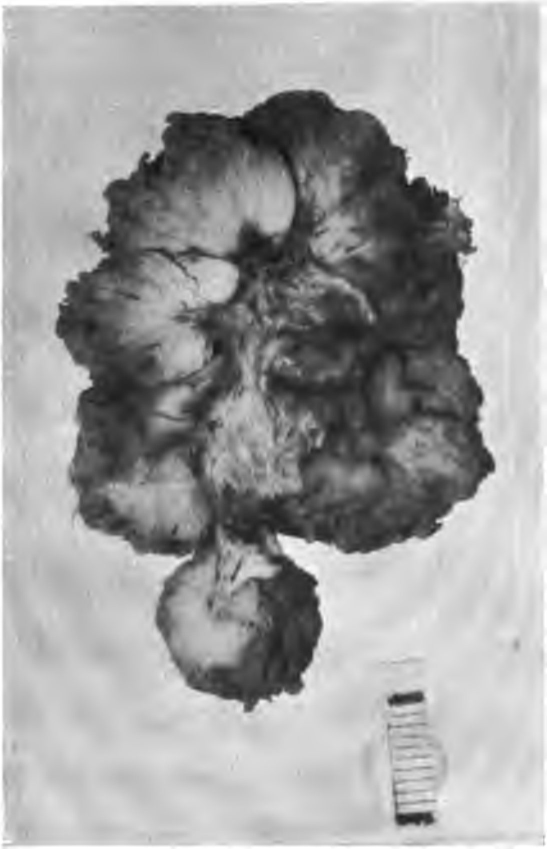


Fig. 109.—Case No. 44996. Section through largest growth in Fig. 108. Showing attachment and blood-supply of the outgrowths.

bladder. By the natural contractions which force the urine out through the urethra these cells were pushed against and grafted on to the mucous membrane at this point.

Treatment.—The treatment of tumors of the bladder consists of removal by incision and cautery and removal by cautery alone.

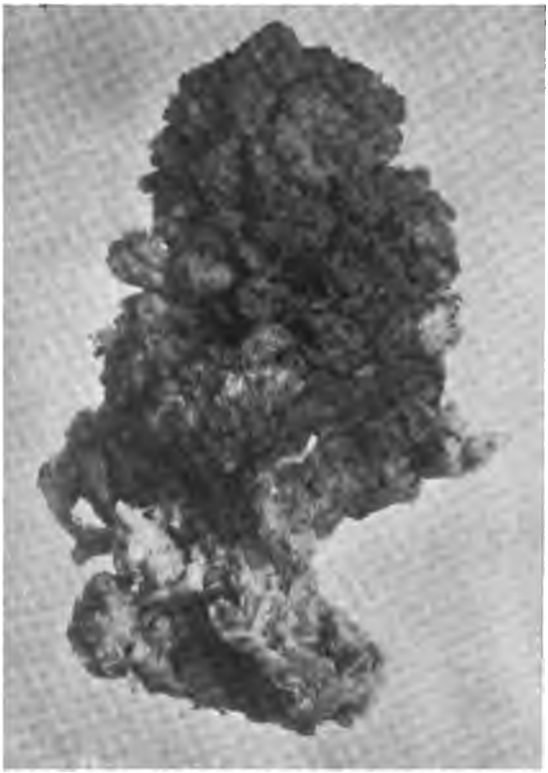


Fig. 110.—Case No. 29510. Upper half shows malignant papilloma of bladder. Lower half shows bladder-wall and surrounding fat.

If the case be obtained reasonably early and the individual be in good condition otherwise, removal by a radical excision of the tumor with a good-sized piece of the wall of the bladder at its base is always the method of choice. This should be done through a suprapubic incision. If the lesion be high on either side or at the dome, it will not be necessary to open the peritoneum, but if the tumor be on or near the base,--and a large percentage of the tumors are in this region,—it is always advisable to open the peritoneum to obtain better exposure and thus do a more complete operation.

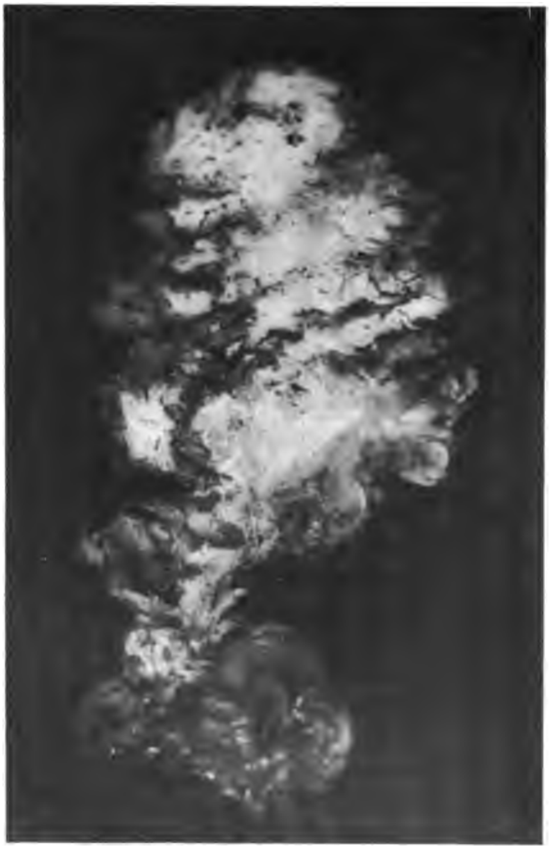


Fig. 111.—Case No. 29510. Section through Fig. 110. Growth arising from wall of bladder is shown in upper half of picture. Wall of bladder is seen in center.

The tumor should be excised with a cautery, or the cut edges of the wall of the bladder should be cauterized after its removal. At the present time there is no argument in favor of the perineal or vaginal incision. A cleaner, more thorough excision with surer functional results and less risk to the patient can be done suprapubically.

For treating small, multiple papillomas, especially in patients with infected kidneys or who are in otherwise bad general condition, the Nitze high-frequency current operated through a cystoscope will accomplish good results. This is an exceptionally valuable method for treating recurrences, which are apt to be multiple and small.

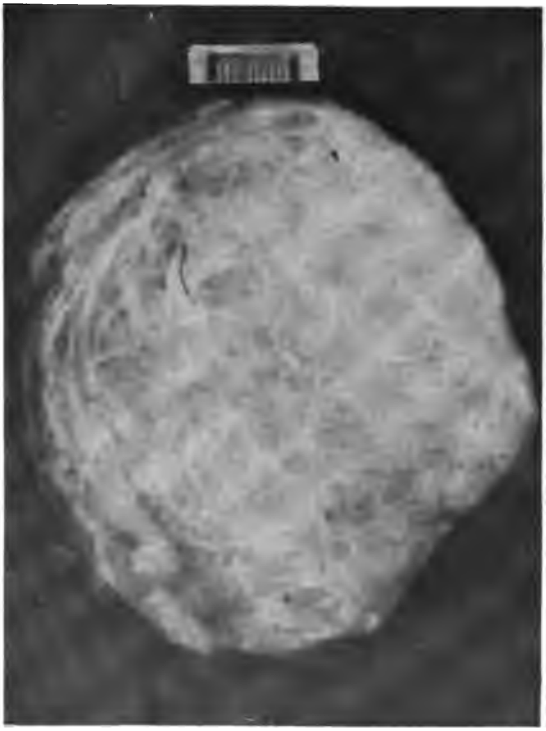


Fig. 112.—Case No. 44496. Section through fibromyoma of bladder.

During the past few years it has been our custom to instruct all patients operated on for tumors of the bladder to return every three to six months for cystoscopic examination. In this way we see any recurrences in the beginning, and by the application of the current are able to keep down suspicious granulating spots, and patients are kept comfortable for an indefinite length of time.

Up to the present time (May 1, 1912) 28 transperitoneal excisions have been performed in our clinic. In 9 of these cases it was necessary to reimplant one ureter, since it was involved at its point of entrance into the bladder. There were 33 suprapubic excisions.

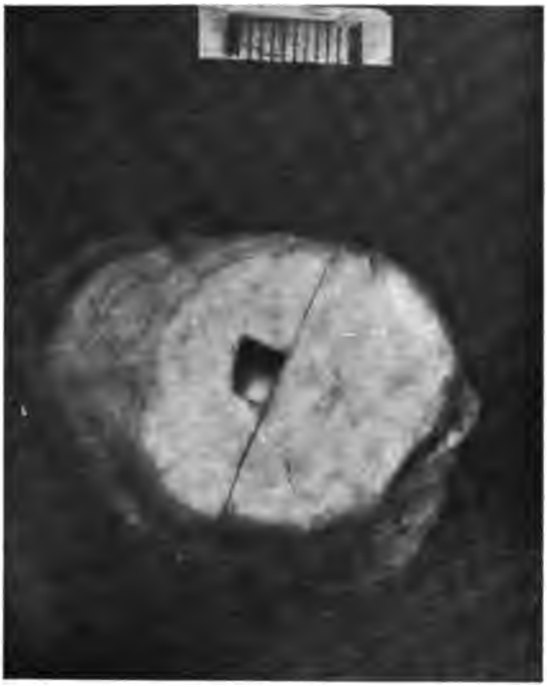


Fig. 113.—Case No. 44028. Section through fibromyoma of bladder. (Block has been removed from center.)

TABLE IV.—OPERATIONS

Suprapubic	33
Transperitoneal	28
Transperitoneal, exploratory	4
Vaginal cystostomy	2
Perineal drain	2
High frequency	1
Inoperable	42
Complete removal of the bladder	2
	114

The comparatively poor results obtained in the treatment of tumors of the urinary bladder are due largely to the fact that the condition is of long standing and therefore too extensive to eradicate thoroughly. In no pathologic condition is early treatment more important than in these vesical tumors. As regards the ultimate cure: A small percentage of patients are absolutely cured, though many of them can be given a considerable prolongation of life and kept comfortable while they live.

RESULTS OF FULGURATION

Seventeen growths were treated by fulguration. This number included 11 cases of recurrence which had been operated in the Mayo Clinic and elsewhere. Five of these were examined one year later and found to be well.

Fifteen months was the longest time any case was under observation after fulguration.

Microscopic reports obtained in 11 cases. But 2 of these were non-malignant.

Only recurring growths treated.

Non-papillomatous carcinoma excluded, particularly if covering large areas.

Large and numerous papillomas excluded.

Number of treatments, 3 or 4.

THE FUNCTIONAL RESULTS IN PROSTATECTOMY *

E. S. JUDD

The prostatic gland is a part of the sexual apparatus, and as such has a definite function to perform. This function is to secrete a substance which is an important ingredient of the spermatic fluid and which is essential to the motility and life of the spermatozoa. Beside the secreting tissue, the gland is also composed of muscular tissue which contracts and expels the secretion, forcing it into the urethra.

At one time it was believed that the intrinsic muscles of the prostate acted in controlling the outflow of urine from the bladder, but this hypothesis has been practically disproved. It is a well-known fact that, after complete removal of the gland and its muscles, the urinary control remains unchanged.

The prostatic gland is rich in nerve-fibers, ganglion-cells, and nerve-end organs, and an interesting relationship exists between it and the testicles. The gland continues to develop up to the age of puberty. If the testicles are lost in childhood, the development of the prostate is stopped, or, if an adult be castrated during the active period of life, the prostatic gland atrophies. The knowledge of this fact led to the Ram-White operation, *i. e.*, castration for hypertrophy of the gland. This, however, appears to be a mistaken procedure, since the atrophy which takes place after castration is an atrophy only of the active, functionating part of the gland. Castration has no effect whatever on the ordinary so-called hypertrophy, which is in reality a tumor-formation and not a true hypertrophy.

---

*Read at the thirty-first annual meeting of the South Dakota State Medical Association at Mitchell, May 22 and 23, 1912. Reprinted from "Journal-Lancet," September 1, 1912, pp. 458–462.

Inasmuch as the prostatic gland has chiefly only a secretory function, its removal will not influence the sexual power, except to interfere with the existence of spermatozoa. We are often questioned by patients regarding the effect removal of the gland will have upon the sexual power, and very often an individual just beginning to notice weakness will ask for an operation with the idea that it will restore function. Since the removal of the gland will not influence the sexual power one way or the other, the

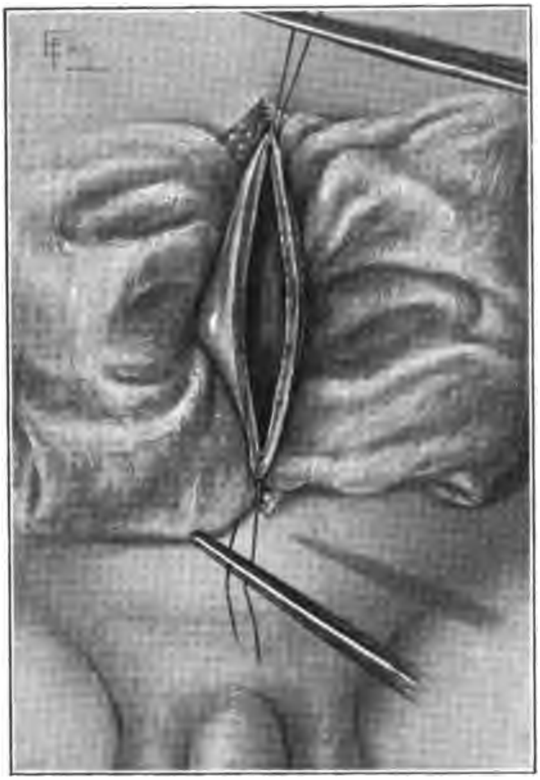


Fig. 114.—Bladder lifted out of the suprapubic wound by the suture in each end of the incision. The edges of the wound are protected by pads of gauze.

patient should be told that, in this respect, he will remain as before the operation. It can readily be seen that preservation of the seminal ducts will act only in providing an escape of the contents of the seminal vesicles and will not have a direct effect upon the function.

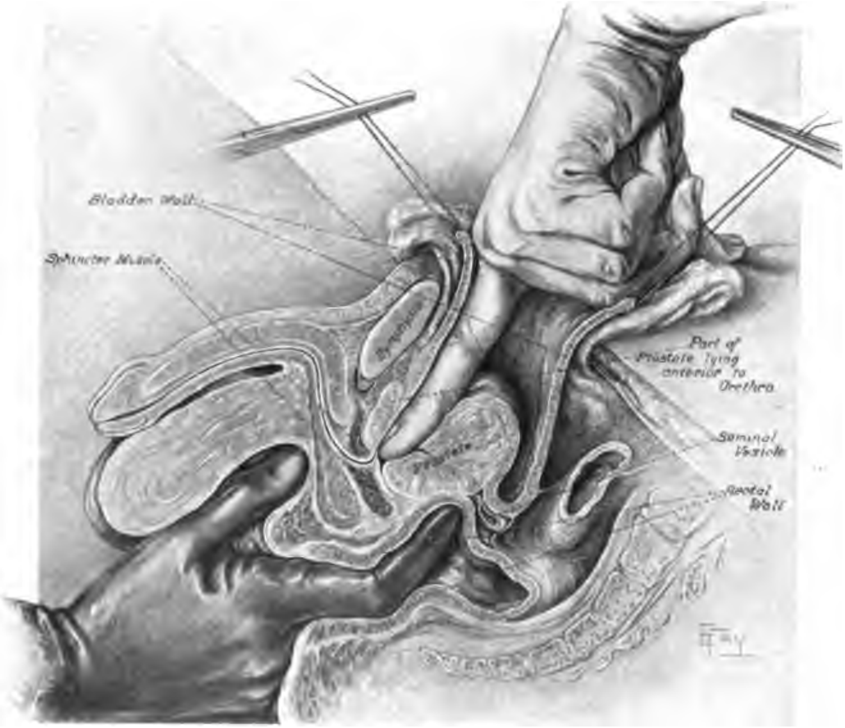


Fig 115.—The forefinger of the gloved right hand in the rectum pushing the prostate up into the bladder. The forefinger of the left hand entering the prostatic capsule through the prostatic urethra. (Elaborated from suggestive sketch illustrating "The Choice of Operation for the Relief of Prostatic Dysuria and the Preliminary Treatment Indicated." Dr. Paul M. Pilcher, "Jour. Mich. State Med. Soc.")

The frequency of micturition which accompanies almost every case of enlargement of the prostate is due not only to the increase in the size of the gland, but is directly proportionate to the amount of existing inflammation and cystitis.

Following prostatectomy the patient is usually obliged to void urine frequently, and this condition exists so long as any granulating surface remains in the capsule from which the gland was removed. When this surface has become entirely healed, the intervals between voiding urine will gradually lengthen, and unless a chronic cystitis exists, the intervals become nearly normal in the majority of cases. The degree of pain also depends largely upon the extent of the cystitis. The pain due to obstruction by the gland will be relieved at once by the removal of the gland. Occasionally, extreme spasmodic pain exists. This is usually caused by a foreign substance in the bladder, or a tag of the gland or mucous membrane which the muscular contractions of the bladder are endeavoring to expel. If there be no preëxisting cystitis and the gland is completely removed, there will be little or no pain remaining by the time the wound in the bladder is healed.

The more important feature as regards these cases in their functional results is their ability to control, absolutely, the outflow of urine. This one factor is almost as important as the ultimate result of the operation. (Many patients tell us they would rather not live than live and be unable to control their urine. A catheter-life is much to be preferred.)

Incontinence may exist before operation, and, with some of these patients, control will improve by removal of the gland, though oftentimes they are made worse. The condition may exist as: (1) Dribbling, constant or intermittent; (2) inability to control while standing or, in some cases, just the opposite, *i.e.*, inability to control while lying down; (3) complete incontinence without knowledge that the urine is escaping (Fig. 114).

The mechanism of urinary control is not well established. Undoubtedly, the internal sphincter and the detrusor muscles are important factors. It is interesting, in this connection, to recall the case operated on by Freyer, which came to autopsy some months later. It was found that the entire internal sphincter muscle had been removed, and yet this patient had just as good control as before the operation.

It has been definitely demonstrated that incontinence does not follow the suprapubic operation (Fig. 115). The control in these cases is as prompt and absolute as at any time, and this is true even if the entire prostatic urethra be removed with the gland. Loss of control after the perineal operation occurs in a small percentage of cases. The condition is most difficult to remedy, and this one feature is a strong argument in favor of the suprapubic operation. We have not observed a case of incontinence following several hundred suprapubic operations, while in as many perineal operations we have observed a number of cases.

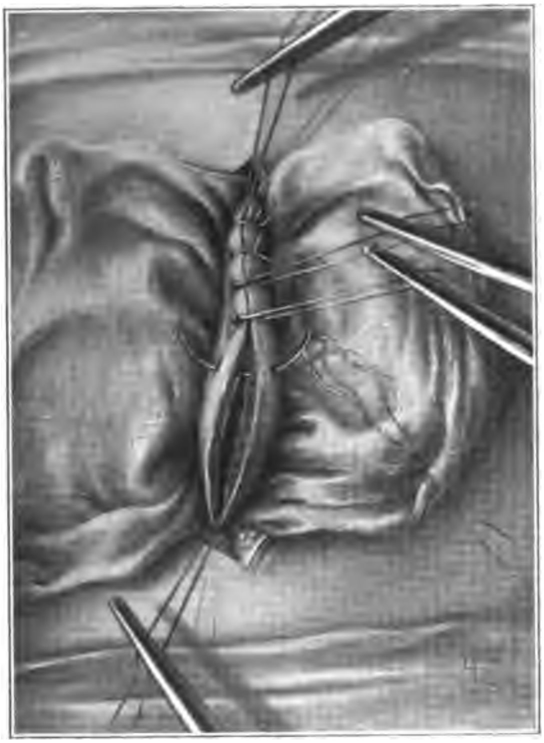


Fig. 116.—The bladder supported in the wound by traction sutures in the ends of the incision. The bladder being sutured by interrupted catgut suture. The sutures include all the coats except the mucosa.

The Alexander exercises may be helpful in these cases. The exercises are recommended on the supposition that the poor con-

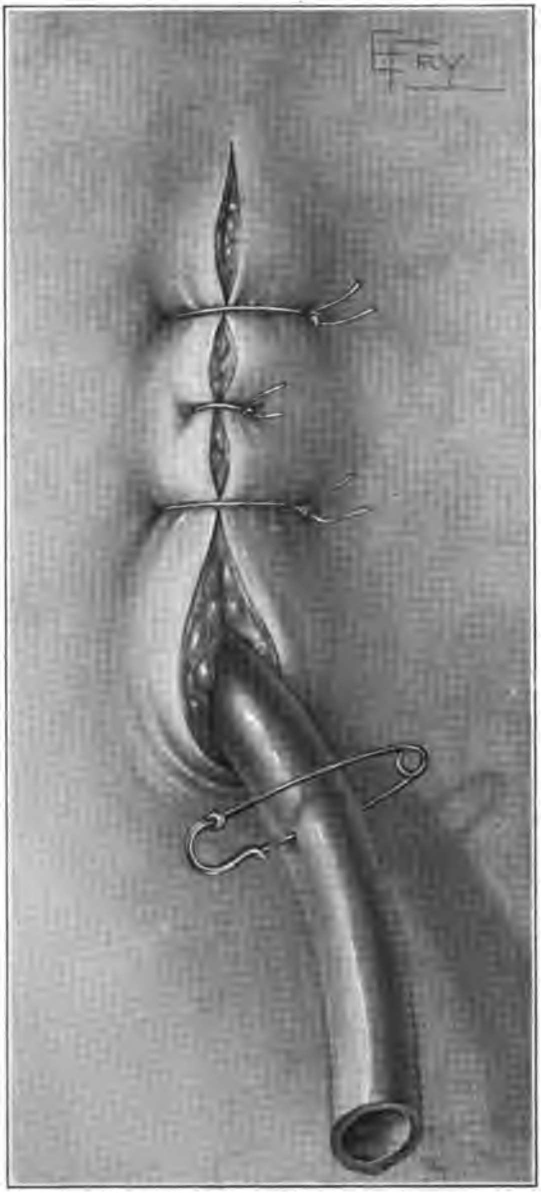


Fig. 117.—The skin closed loosely. Rubber tube drain in the space of Retzius.

trol is due to a lax muscle. The details are as follows: The bladder is filled with a solution of boric acid, and the patient is instructed to pass a part of it and then stop, holding the remainder as long as possible, then passing a little more, and so on until the bladder is empty, in this way exercising the weakened muscle. These exercises should be repeated several times each day.

Inability completely to empty the bladder after the prostate has been removed may be due to atony of the muscles of the wall of the bladder, which is essentially due to a nerve-lesion, or it may be due to incomplete removal of the gland, so that some obstruction still exists. If there be no existing nerve-lesion, such as tabes, and the gland be entirely removed, there will be no residual urine.

Since every enlarged prostate does not cause an obstruction, and since it is frequently difficult to prove the existence of a nerve-lesion, and, furthermore, since the residual urine may be due partly to mechanic obstruction and partly to atony, it is sometimes difficult to know before operation just how effectually the residual urine will be relieved by the removal of the gland. To determine this point more accurately, Crenshaw (Mayo Clinic) devised a method of measuring the muscular power of the wall of the bladder against a mercurial column. The normal contracting power is determined and a standard established by measuring the expelling power in a number of normal bladders. The obstruction can be relieved by introducing a catheter into the bladder: the contracting bladder exerts pressure on the fluid contents, and the amount of this pressure is measured in a manner similar to that of measuring the blood-pressure.

The length of time required to heal a urinary fistula varies considerably. Following the perineal operation, the fistula usually heals in from ten to twenty-one days. Following the suprapubic operation, the fistulas are often very slow to heal and sometimes require many weeks. Permanent fistulas are usually due to a stone or tumor, or to a remnant of the gland in the bladder.

Recently we have endeavored to close the wound in the bladder completely when doing the suprapubic operation. This method has been most satisfactory in cases without a great deal of cystitis and if there be but little hemorrhage. The bladder is afterward drained by a catheter through the urethra, which will require constant irrigation until the urine comes clear and free from clots.

The catheter, with frequent changing, should be left in the bladder about twelve days. After removing the gland and washing all clots from the bladder, the coats of the organ, with the exception of the mucous membrane, are sutured by interrupted sutures (Fig. 116). The suprapubic operation should not be done if there be much infection or hemorrhage, but if it can be done, about one-half of the cases will heal without leakage, and the patients will be more comfortable and will have a short convalescence (Fig. 117). If the wound does not break open, there will be little drainage after several days, and little or no infection following these operations.

PROSTATECTOMY*

E. S. JUDD

Until within the past few years the perineal operation for removal of the hypertrophied prostate was the operation of choice in many hospitals in this country. As an advocate of this method I would argue, first, that the mortality is less, and, second, that the time of convalescence is shorter, since the perineal wound heals much more quickly than the suprapubic. Studying the cases more carefully, however, we have found that the mortality is not directly a result of the operation, but that it depends upon the functional capacity of the kidneys and the condition of the heart and general circulation, which is true with either operation. The mortality has been greatly reduced by proper preparation of the patient before operating.

For a number of years we have advocated dividing the treatment into two stages:

First Stage.—The first stage consists of relieving the patient of the residual urine and at the same time treating the cystitis, if it exists. Whether it is the mere presence of residual urine in the bladder or whether it is the backward pressure of the urine upon the kidneys which produces the deleterious effect I cannot say, but we are all aware of the harm that may be done by keeping the bladder empty when it has been accustomed to retaining even a few ounces of residual urine. We believe that the urine which is retained in the bladder should be withdrawn gradually, keeping the bladder empty for a longer period each day until no bad effects are apparent. In many instances it will require several weeks to carry out this treatment, but it invariably results in a most marked change for the better in the general condition of the patient. In about three-fourths of the cases the requisite drainage has been accomplished by means of a permanent catheter introduced into the bladder through the urethra. In the remaining one-fourth of the cases it was necessary to make a preliminary suprapubic stab drain, because it was impossible to introduce a catheter or because the urethral catheter could not be worn with any degree of comfort.

---

*Read before the Clin. Cong. of Surg., November 15, 1912. Reprinted from "Surg., Gyn., and Obstet.," April, 1913.

Second Stage.—After the reaction due to the withdrawal of the urine has passed, the specific gravity, which invariably falls with the introduction of the catheter, will again come up, and the second stage of the treatment, *i.e.*, the removal of the obstructing prostatic gland, can be carried out. This procedure will be accomplished more satisfactorily and with more safety than if the preliminary treatment had not been instituted.

The functional result as regards the ability of the patient to empty the bladder, and, far more important, his ability absolutely to control the flow of urine, is the most important factor in the treatment of these cases. This result is attained in the perineal operation in a large percentage of the cases, but it is quite impossible to determine which will have poor control or which will have complete incontinence. In none of our cases following the suprapubic operation has there been any difficulty absolutely to control the stream, and in practically all of them the bladder can be emptied completely.

The work of Tandler and Zuckerkandl,[1] and, more recently, the studies of Lowsley relating to the development of the prostate, have shown that the middle lobe is independent, and is the one which most frequently undergoes changes in a so-called hypertrophy. Lowsley[2] has shown that the anterior lobe shrinks into insignificance at the twenty-second week, but that this structure may persist throughout life, as is evidenced by the occasional finding of enlarged anterior lobes at autopsy. The same author has also demonstrated that the posterior lobe of the prostate is an independent structure. Its tubules originate from the floor of the prostatic urethra, below the openings of the ejaculatory ducts, and are definitely separated from the other parts of the gland. A fibrous capsule intervenes between this lobe and the lateral lobes. In their investigations on prostatic hypertrophy Tandler and Zuckerkandl did not find the posterior lobe enlarged in a single instance, but found a condition of *pressure-atrophy.*

Boyd and Geraghty[3] state that primary carcinoma of the prostate rarely or never begins in any other part than in the posterior lobe. In operating through the bladder, this lobe is not disturbed, a point of practical value because of the close relation of this lobe to the ejaculatory ducts. In the ordinary suprapubic operation for a benign hypertrophy the ejaculatory ducts are not injured in any way, and the sexual state remains exactly as it was before the operation.

The chief disadvantage in the suprapubic method is the length of time required for the urinary fistula to heal, due to infection in this poorly resisting suprapubic space. It has not been uncommon to see these cases drain for weeks or even months, or to see a case terminate badly on account of extensive infection. In every other respect I believe the suprapubic operation is to be preferred, and within the past few years have operated almost entirely by this route. By changing some of the minor points in the technic of the operation I have endeavored to remove the gland with as little chance as possible of infecting the suprapubic tissues. After the gland is removed, the incision in the bladder is drained or closed in such a way that the tissues are exposed as little as possible to infection.

Technic.—The abdominal incision is made in the usual way, and the recti muscles are separated. It is much better to make a large incision than to try to work in a crowded space. The fat in the suprapubic space is dissected off from the fundus of the bladder and the peritoneum pushed back. It is very essential that the peritoneum be stripped well back and that the bladder be lifted up as far out of the abdominal incision as possible. It is preferable to have the bladder empty, since it has not been found advantageous to fill it with air or water, or to open it on a sound. Ordinarily, the peritoneum is not opened, but is stripped back from the bladder. Occasionally, however, the peritoneum will be opened accidentally. This may occur in separating it from the bladder or it may be done by the pressure used in shelling out a low-lying gland. The first few times this accident occurred I was extremely fearful, but I have now opened the peritoneum in seven cases, each time closing the opening with catgut as soon as it was discovered. In none of these instances did it make the slightest difference in the convalescence of the patient (Fig. 118).

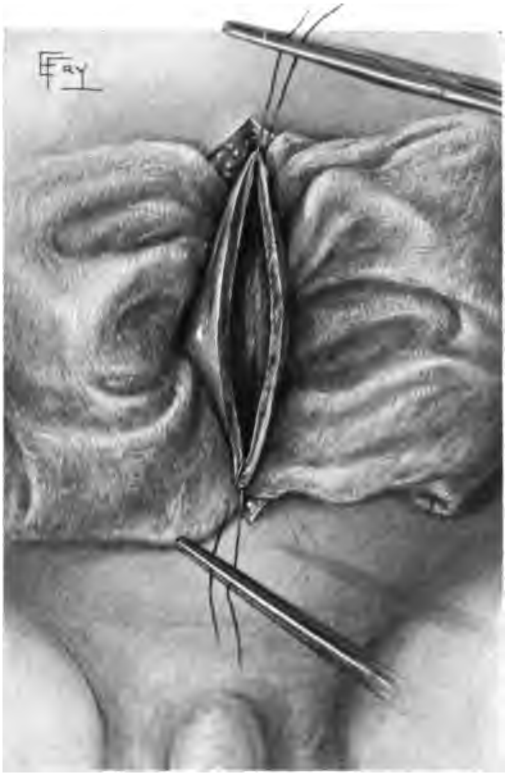


Fig. 118.—Bladder lifted out of suprapubic wound by suture in each end of incision. Edges of wound protected by pads of gauze.

With the fundus of the bladder lifted well out of the abdominal incision, the abdominal wound is packed off with gauze; the bladder, which a few minutes before has been cleaned as thoroughly as possible, is now opened by free incision, usually about 2 inches in length. As soon as this opening has been made, a supporting suture is passed through each angle of the incision in the bladder and the organ dried by sponging out any accumulated urine or water used in cleansing. It is well at this stage of the operation to examine the bladder for stones or other lesions. This is especially important if it has not been possible to make a satisfactory cystoscopic examination (Fig. 119).

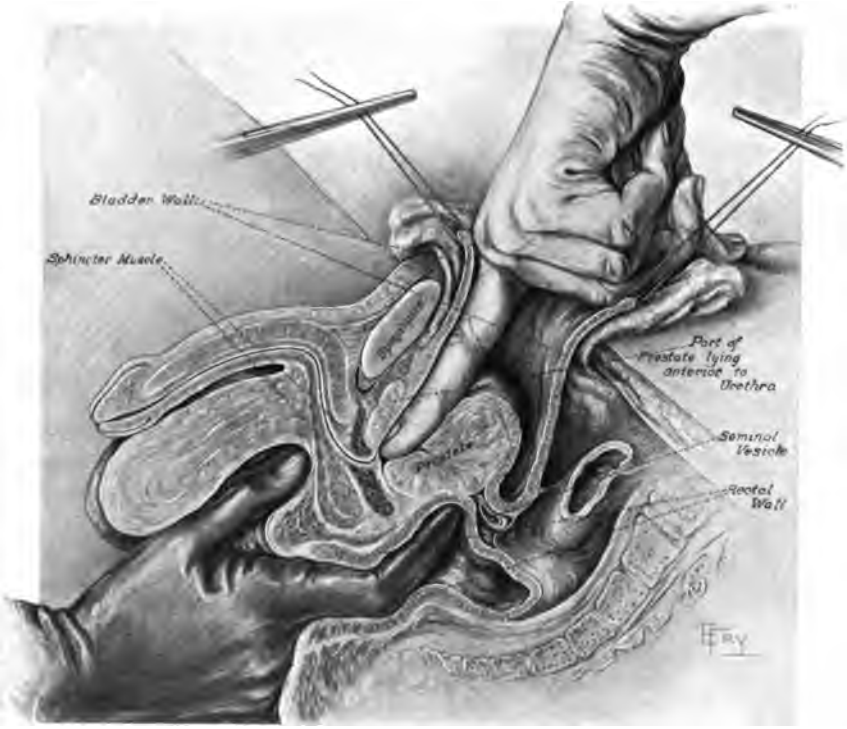


Fig. 119.—Forefinger of gloved right hand in rectum, pushing the prostate up into the bladder. The forefinger of left hand entering prostatic capsule through prostatic urethra. (Elaborated from suggestive sketch illustrating "The Choice of Operation for the Relief of Prostatic Dysuria and the Preliminary Treatment Indicated," by Dr. Paul M. Pilcher, "Jour. Mich. State Med. Soc.")

With the gloved fingers of the right hand in the rectum, the gland can be pushed well up into the bladder. The first and, if necessary, the second fingers of the left hand are introduced into the bladder. I prefer to start the shelling out of the gland by breaking into the prostatic capsule with the bare finger, rather than by using an instrument to cut into it. In some instances, however, especially when a catheter has been used for a great many years, the mucous membrane of the prostatic urethra may have become so toughened that it will be necessary to start the enucleation by cutting through this membrane, since to break through would cause too much traumatism. Ordinarily, the finger pushed into the prostatic urethra very quickly breaks into the capsule. Oftentimes, on either side of the prostatic urethra the hypertrophy rounds into the urethra, and this makes a convenient place to start the enucleation. If necessary, the entire circle of prostatic urethra may be removed. It will reform quickly, and there is no danger of the formation of stricture. On a number of occasions the entire circle of prostatic urethra has been removed. It is customary, however, to start shelling out the gland at one lateral aspect of the urethra, and to terminate at a point about opposite. This saves a strip of mucous membrane of the prostatic urethra running along the dorsum between the bladder and the membranous urethra, and insures against any possible stricture formation. This would seem to be a saving in time for a reëstablishment of the entire prostatic urethra. The enucleation should include the entire prostate gland, with the exception of the small piece lying in front of the prostatic urethra, and the posterior lobe lying behind.

For several reasons it is most important that practically the entire gland be removed, and the fact that the entire gland can be removed by this method is probably one of the best arguments in favor of the suprapubic over the perineal route.

The prostate is entirely surrounded by the fibromuscular capsule. When the gland has been completely enucleated, the capsule contracts quickly, and the hemorrhage stops in a very short time. If, however, a piece of the gland be left in the capsule, it acts the way a piece of retained placenta acts, *i. e.*, interferes with the contraction of the capsule and thus keeps up the bleeding. The hemorrhages in these cases have been a source of anxiety to surgeons, and many devices have been shown to control them. At the present time, however, I believe that if enucleation be

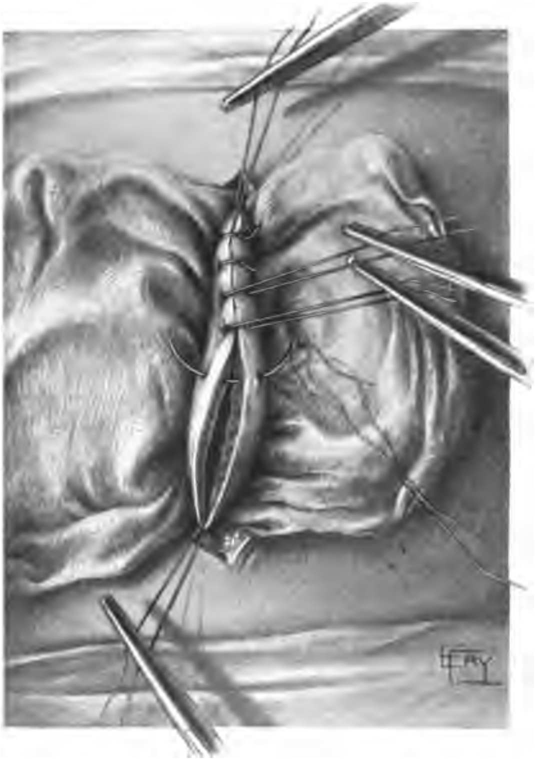


Fig. 120.—Bladder supported in wound by traction sutures in ends of incision. Bladder being sutured by interrupted catgut suture. Sutures include all coats except mucosa.

done within the capsule and the prostate be entirely removed, there will be very few cases in which it will be necessary to use even a gauze pack to stop the bleeding. Sharp hemorrhage may be caused by dissecting outside the capsule into large vessels or by leaving a piece of the prostate in the capsule. If the enlarged gland be entirely removed, the capsule will contract, and the chief bleeding will be only that which oozes from the edge of the mucous membrane in the urethra and bladder. As soon as the gland is shelled free from its capsule and the urethra is torn off, the catheter, which was introduced into the urethra before the operation was begun, is passed through the prostatic capsule into the bladder and irrigation commenced. The irrigation must be commenced as soon as the gland is shelled out, to prevent the accumulated blood from clotting or to wash out the clots which have accumulated in the

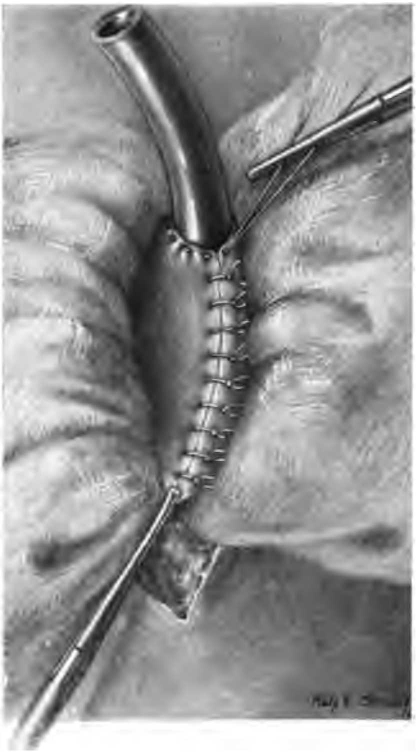


Fig. 121.—Showing rubber drainage-tube held by purse-string suture in upper end of bladder-wound—a method employed when the bladder is badly infected and bleeding seems too free for complete closure of bladder.

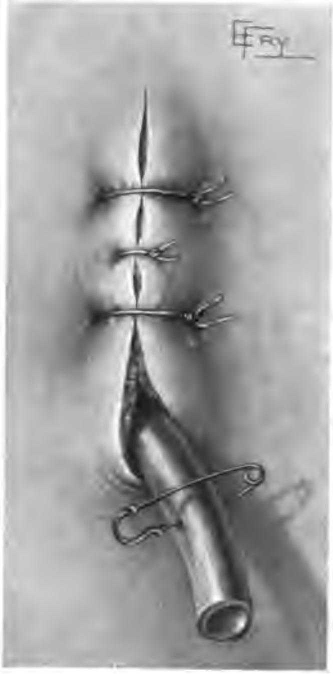


Fig. 122.—Showing method of draining suprapubic space when the bladder has been closed completely. Tube is placed in lower angle of wound and extends downward, between the recti muscles, to the wall of the bladder.

bladder. The first appearance of clots and blood may give the impression that a sharp hemorrhage is about to occur, but if the irrigation be continued a few minutes, the flow clears up, and from then on the bleeding will amount to little or nothing. Free

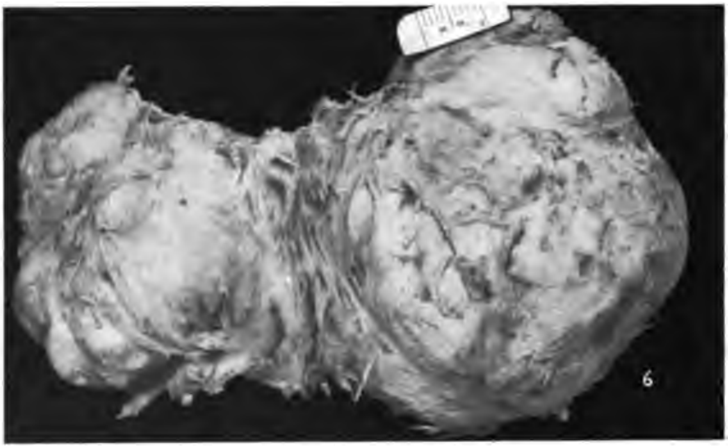


Fig. 123.—Anterior view of large prostate in which the hypertrophy has produced bilateral enlargement of gland.

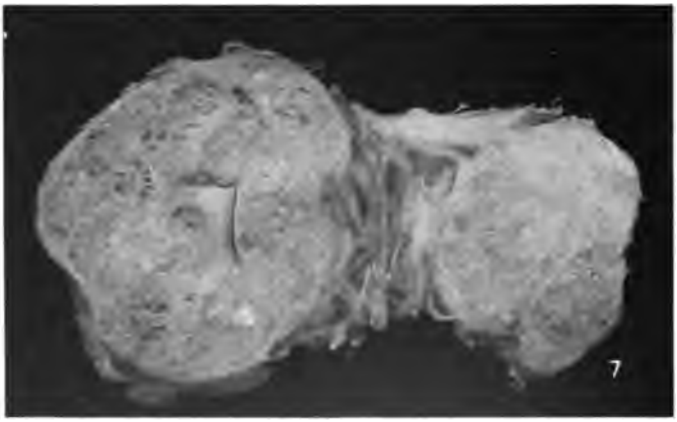


Fig. 124.—Section through specimen shown in Fig. 123, showing glandular type of hypertrophy, with many small cysts in the enlargement seen on left of picture. On the right the enlargement is smaller and contains much fibrous tissue.

irrigation is kept up for several minutes, washing through and through the bladder. The bladder is constantly supported as far out of the wound as possible by the sutures in the two angles (Fig. 120). As the irrigation continues, interrupted sutures of catgut are placed in the incision in the bladder until the wound

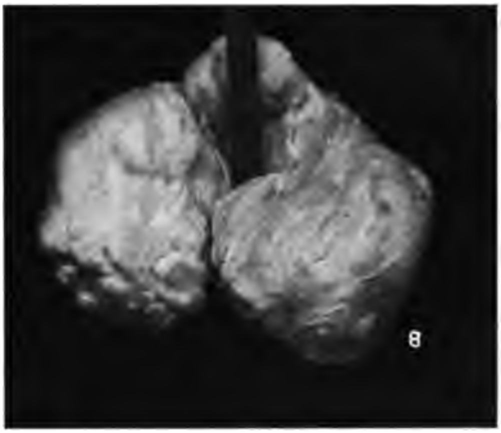


Fig. 125.—Anterior view of prostate in which the hypertrophy has produced two lateral enlargements and a small median enlargement. A catheter has been passed through the prostatic urethra. The median enlargement shows in the upper portion of picture, behind catheter.

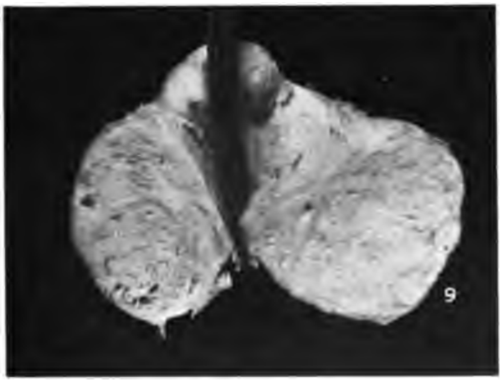


Fig. 126.—Section through specimen shown in Fig. 125. Catheter still shows in prostatic urethra. Glandular type of hypertrophy with considerable amount of fibrous tissue and many small cysts.

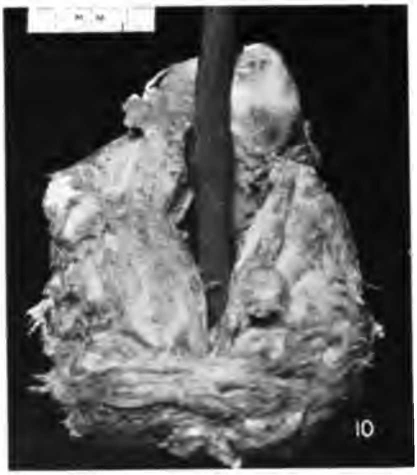


Fig. 127.—Anterior view of prostate, with two lateral and a median enlargement. Catheter placed in prostatic urethra. In lower portion of picture lateral enlargements are held together by tough fibrous band. Urethra passes beneath band, and opening shows on lower border of picture.

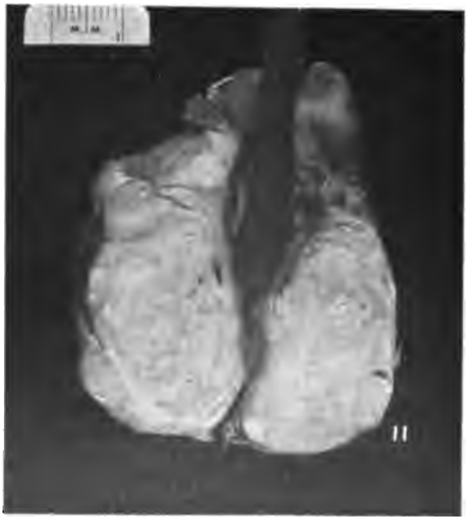


Fig. 128.—Section through specimen shown in Fig. 127. Note the narrowed urethral channel, which will not permit the passage of catheter. Glandular type of hypertrophy with small cysts and much fibrous tissue.

is closed. Just before placing the last sutures the finger is introduced into the bladder, to make sure that there are no clots remaining. Should the oozing continue to an extent to clot the

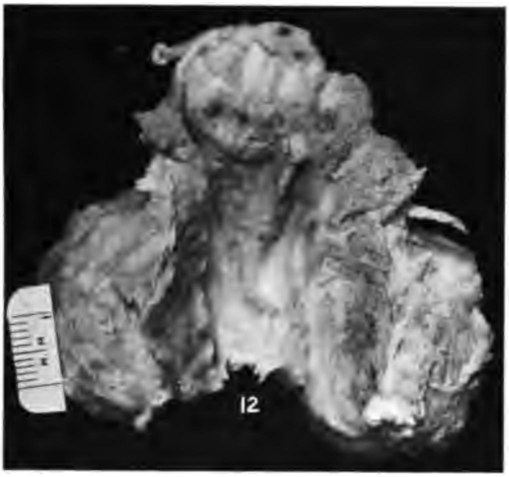


Fig. 129.—Anterior view of prostate in which hypertrophy has produced two lateral enlargements and a median enlargement. Obstruction caused by median enlargement.

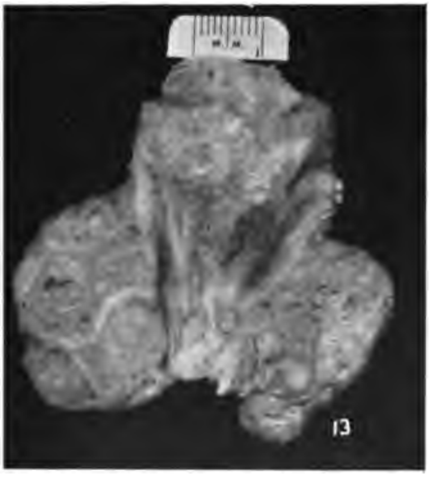


Fig. 130.—Section through specimen shown in Fig. 129. Glandular type of hypertrophy with many small cysts and small amount of fibrous tissue.

urethral catheter while the bladder is being closed, a small tube is introduced at the highest point in the incision (Squier) and

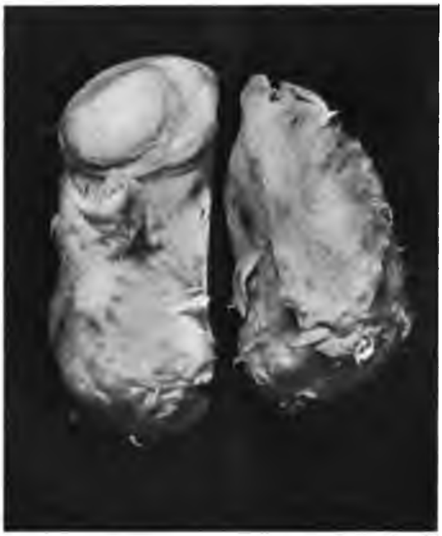


Fig. 131.—(46704.) Anterior view of prostate in which the hypertrophy has produced two lateral enlargements and a median enlargement. A catheter has been passed through the prostatic urethra. Median enlargement shows above to left of catheter.

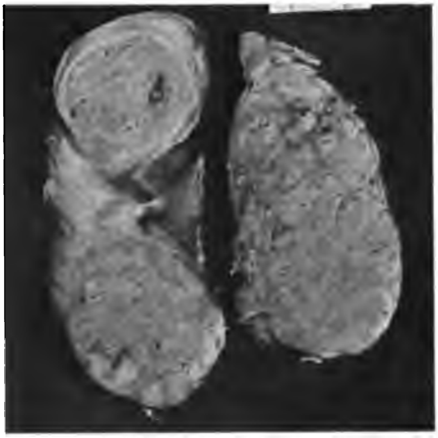


Fig. 132.—(67394.) Section through specimen shown in Fig. 131. Note tortuous and obstructed urethral channel. Glandular type of hypertrophy with many small cysts.

the irrigation made continuous, passing through the catheter and

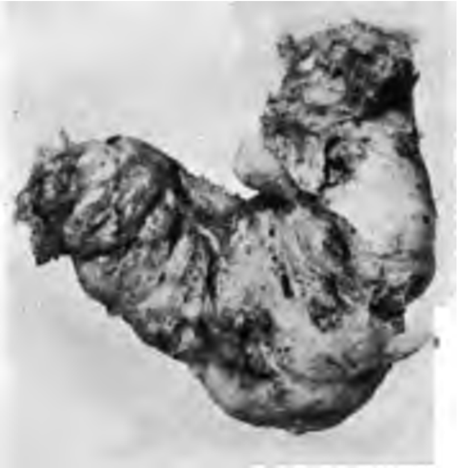


Fig. 133.—(42386.) Large irregular shaped prostate which weighed 8 ounces. Hypertrophy has produced two lateral enlargements which projected high into the bladder. Urethral channel passes through bottom of concavity which shows in upper portion of gland.

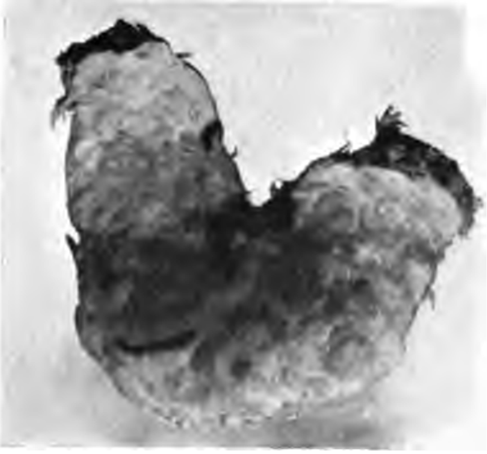


Fig. 134.—(42386.) Section through specimen shown in Fig. 133 (unfixed specimen). Urethral channel passes through bottom of concavity shown in upper portion of the gland. Glandular type of hypertrophy with bulging adenomatous areas.

out of the suprapubic tube (Fig. 121). This tube should be sutured accurately into the bladder in the same manner that the tube is sutured into the gall-bladder to prevent leakage. As soon as the patient is put in bed, constant irrigation is commenced and kept up until the cleansing water is clear. This will ordinarily take twenty-four, sometimes forty-eight, hours. The tube is then removed. In many of the cases there will be little or no drainage from the wound afterward.

The bladder is washed frequently through the urethral catheter, which is left in place until the wound above has remained closed for several days. When the sutures have been placed in the bladder, if there is no difficulty due to clots, and if the cleansing water is returning clear through the urethral catheter, the wound in the bladder is closed completely and a small tube introduced to drain the suprapubic space (Fig. 122). If the bladder be completely closed, it is necessary to have either a two-way catheter for constant irrigation or have a nurse syringe out the bladder every few minutes until all signs of oozing have stopped. In some of our cases there has been difficulty from clots during the first few hours following operation, though usually frequent irri-

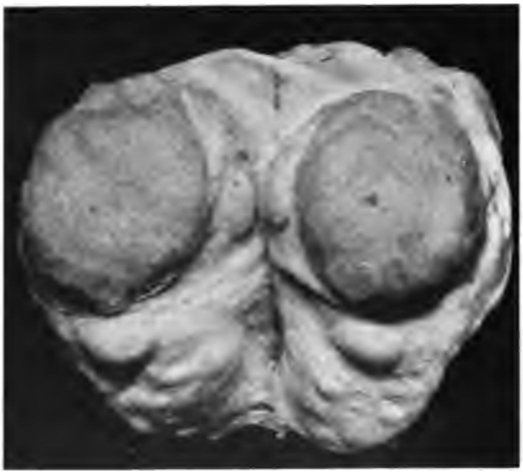


Fig. 135.—A lateral enlargement, from a prostate which has been opened and photographed in unfixed state. A large adenomatous area has been sectioned and shows in each half. Similar smaller areas also show. In unfixed specimens these adenomatous areas protrude or bulge outward after the fibrous tissue surrounding them has been cut.

gation and the use of alum water will stop the oozing, so that at the end of twelve hours it will not be necessary to syringe out the bladder oftener than once every hour. When the cleansing water returns clear, the first catheter is removed, and a clean, sterile one reintroduced. It may require some adjusting to place the catheter in the proper position in the bladder so that spasms will not occur. However, the majority of the cases are entirely comfortable with the catheter in position. The catheter should be changed frequently, but should be kept in the urethra until the suprapubic wound has remained entirely healed for several days. This will usually take from two to three weeks.

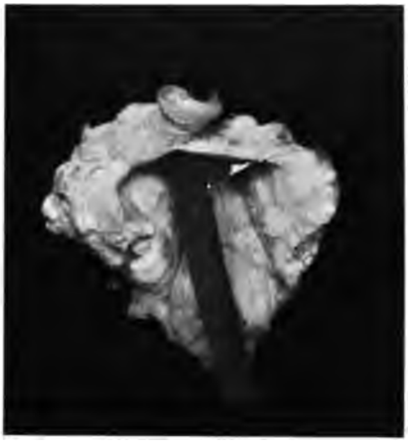


Fig. 136.—Small fibrous prostate with slight hypertrophy. Obstruction caused by median enlargement, which shows in upper part of picture, behind catheter. A tough fibrous band surrounding urethral canal shows in lower portion of picture.

Two or three silkworm-gut sutures are placed in the abdominal wound, the recti muscles being included. This wound is not closed completely. But few of these wounds heal by absolute primary intention—there will be a little serum drainage and, in some cases, urinary leakage for two or three weeks. A few cases have occurred in our clinic in which the suprapubic space became infected in much the same way that followed after the old method of packing the wound with gauze.

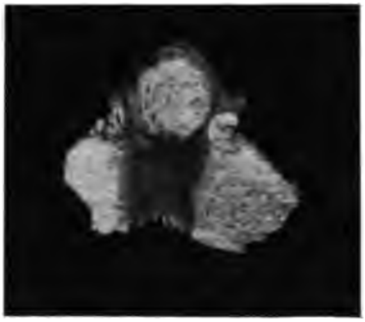


Fig. 137.—Specimen shown in Fig. 136, on section. Dark area in center of picture is prostatic urethra. Median enlargement which caused obstruction shows in upper portion of picture. Glandular hypertrophy with small cysts and much fibrous tissue.

The chief points in favor of this technic in the suprapubic operation may be enumerated as follows: (1) Patients are much more comfortable during the period of convalescence; (2) they do not have to contend with the urine-soaked dressing, and (3) the run of temperature due to absorption from infection in this space is avoided. While these patients require considerable care during the first twenty-four hours following operation, after that time they are much easier to care for, requiring very little dressing.

REFERENCES

1. Tandler and Zuckerkandl: "Folio Urologica," March, 1911.
2. Lowsley: "Amer. Jour. Anat.," July 15, 1912.
3. Boyd and Geraghty: *Loc. cit.*
4. Squier: *Loc. cit.*

BENIGN AND MALIGNANT OVARIAN CYSTS *

A REPORT OF 1000 SPECIMENS

WILLIAM CARPENTER MACCARTY AND WALTER E. SISTRUNK

In reviewing the literature on the subject of ovarian tumors, especially ovarian cysts, the writers find that over 1000 articles have been published since 1903. In the light of our present general knowledge of the subject a review of such a wealth of recorded observations would be of only historic interest.

Most surgeons and physicians have a good working knowledge of large cystadenomas and simple cysts, dermoids, the so-called "corpus luteum cysts" (hemorrhagic cysts), and parovarian cysts. These comprise the cysts which are technically most easily diagnosticated and removed. The differential diagnosis of small ovarian cysts is, however, very difficult, but, from a technical standpoint, the differential diagnosis of these has been of no immediate importance to the surgeon.

Cysts smaller than a hen's egg possess qualities which have a wide and very different prognostic significance. The main objects of this paper are to call attention to the possibilities which may arise from these qualities, and to present a synopsis of our findings in a study of a large number of ovarian cysts.

The material used for this investigation consisted of ovaries which had been removed for definite pathologic conditions, and apparently normal ovaries which had been removed during the course of complete hysterectomies for uterine carcinomas. Ovaries removed at autopsy were also used for comparison.

---

* Read before the Canadian Medical Assoc., Edmonton, August, 1912. Reprinted from "Surg., Gyn., and Obst.," July, 1913.

The material which was examined consists of 1000* specimens (from February 3, 1905, to August 1, 1912). The various tumors occurred in the following frequency:

1. Hemorrhagic cysts	214
2. Non-hemorrhagic cysts	451
3. Papillary and carcinomatous cysts	163
4. Dermoids	98
5. Parovarian cysts	74
	1000

The duplicity of ovarian cystadenomas and dermoids can be only approximately determined from surgical material. The surgeon often leaves a small ovary without knowledge of its exact nature or through conservatism. We have records of dermoids occurring in both ovaries 14 times (14 per cent.) in 98 cases, and carcinoma occurring 7 times (7 per cent.) in 97 cases.

For special examination and description, a report, of which this is the first paper, 100 specimens were taken as representative of the 1000 which had been recorded. These represent all the conditions which were seen in this material. Each specimen was photographed grossly, either in its fresh condition or in a fixed condition. Gross sections were made through the whole tumor, and gross photographs were made of these sections. Blocks were then taken, embedded in celloidin, cut, and stained with hematoxylin and eosin.

With our present knowledge of physiologic and pathologic processes and their cognizable signs and symptoms, it is impossible to express diagnostic, macroscopic, microscopic, and prognostic characteristics in a diagnostic term. For this reason a method of reporting ovarian cysts similar to that used in reporting specimens of goiters seems most applicable and will be used in this paper.

The principal distinguishing feature in ovarian cysts is the lining epithelium. This is apparently differentiated or specialized and is most important.

Three different linings are seen, viz.: *Round or oval, many-*

---

* This number does not represent the complete material, but is sufficiently large for a study of the conditions. Solid tumors were not considered in this investigation.

layered epithelium (Fig. 158, *a* and *b*), high or low, *columnar epithelium* (Fig. 158, *d*), and *lutein cells* (Fig. 138). These three types of cells have apparently three different functions. Whether or not

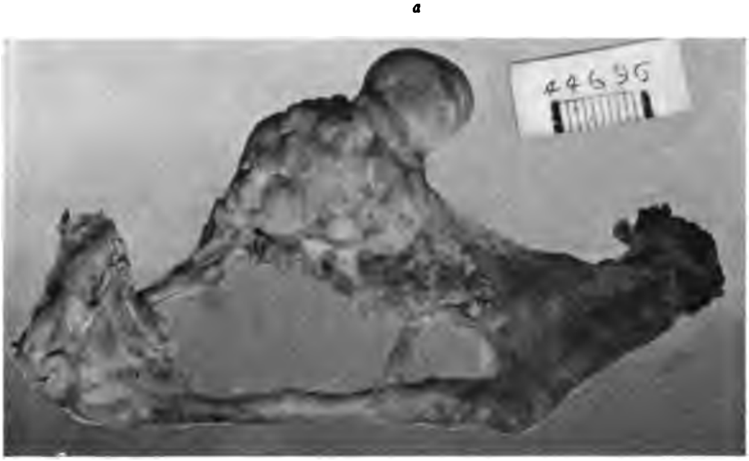


Fig. 138.—A pedunculated corpus luteum (*a*).

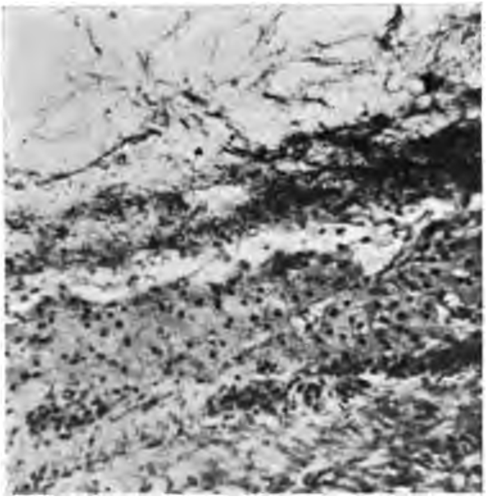


Fig. 139.—Photomicrograph of a section through the wall of a corpus luteum, showing large lutein cells.

the columnar epithelium and the many-layered epithelium may develop from each other is unknown. The only indication that

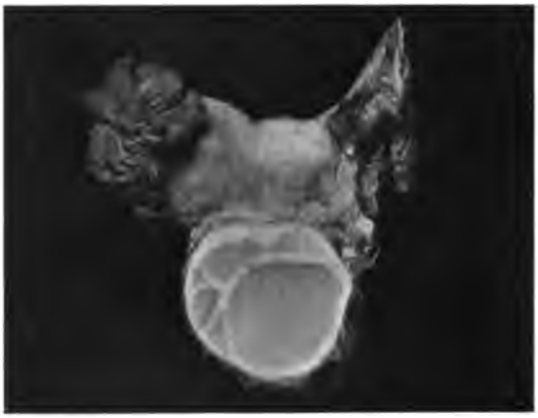


Fig. 140.—Multiple simple ovarian cysts.

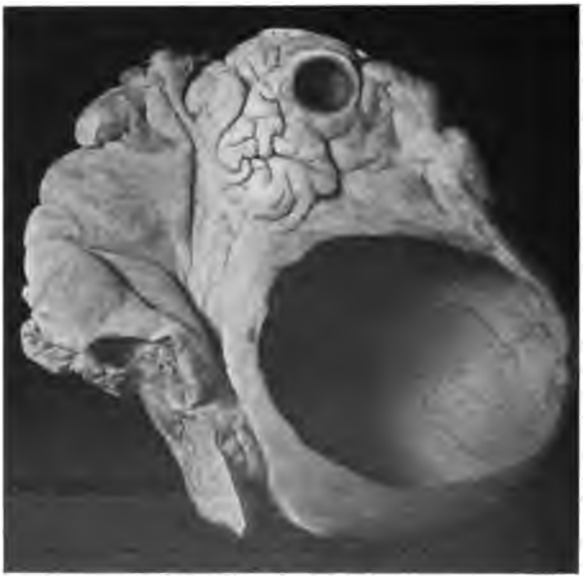


Fig. 141.—Large and small simple ovarian cysts.

this may be possible is the presence of both types in the same cyst (Fig. 147). Upon these fundamentals all neoplastic cysts of the ovary may be classified and described.

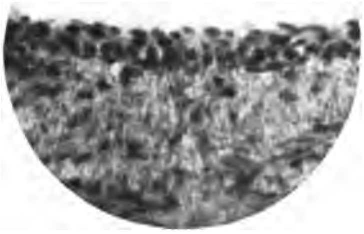


Fig. 142.—Photomicrograph of the wall of a simple ovarian cyst.

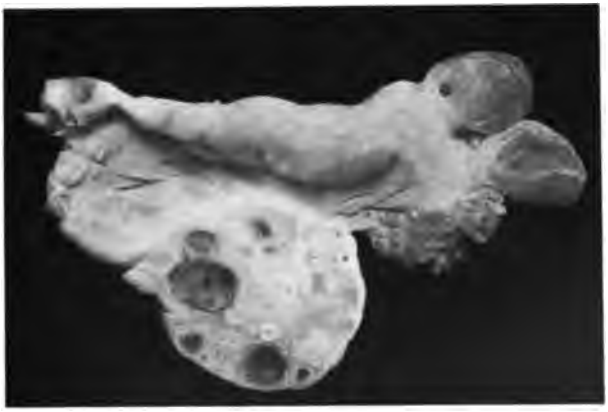


Fig. 143.—Simple ovarian cysts with hemorrhagic walls.

SIMPLE CYSTS

The simplest cyst (Figs. 141 and 142) which one finds possesses a wall, the inner surface of which is smooth and is composed of from two to six layers of small oval or round epithelial cells (Fig. 142). The content of such a cyst is a clear fluid.

When a Graafian follicle ceases to be a follicle and becomes a simple cyst of this description is not known. That such cysts originate from Graafian follicles is to be strongly suspected, because they have a similar lining and contain apparently the same clear fluid. Such a cyst may attain the size of a human

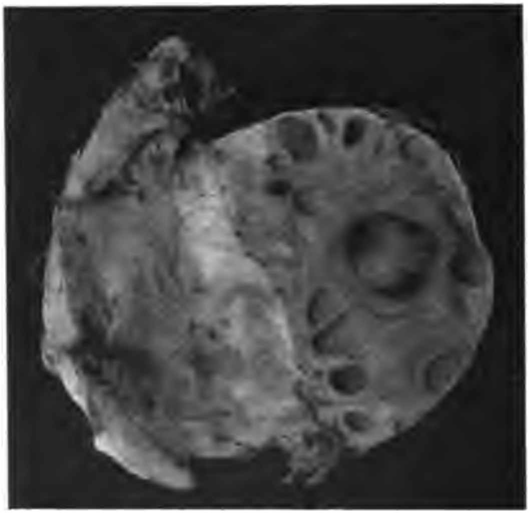


Fig. 144.—Simple ovarian cysts with hemorrhagic walls.

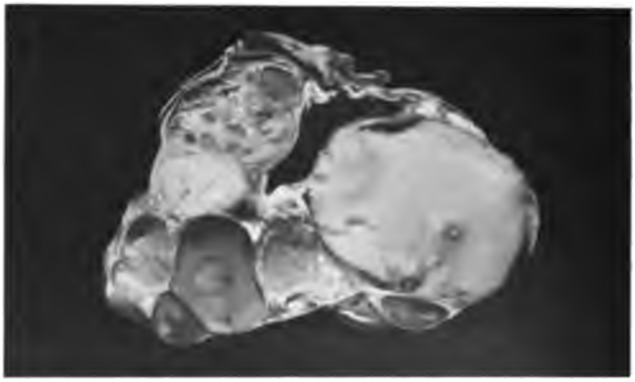


Fig. 145.—Ovarian cystadenoma, showing "pseudomucinous" contents.

head. Their simplicity of structure and contents may allow the utilization of the term "simple cyst," in contradistinction to the apparently more highly differentiated cyst, which is lined by columnar epithelium (Fig. 158, *c*, *d*, *e*), and which secretes a complex, highly albuminous fluid.

The secondary descriptive features of simple cysts consist in their being unilocular or multilocular, and whether or not hemorrhage has occurred into the wall or into the interior (Figs. 143, 144, 148, and 149). They may be briefly described in pathologic reports as follows:

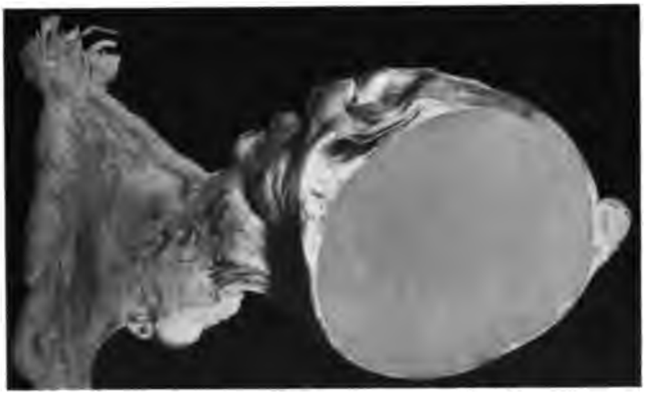


Fig. 146.—Ovarian cystadenoma from the same case, but from the opposite ovary.

$$\text{Simple}\left\{\begin{array}{c}\text{unilocular}\\ \text{or}\\ \text{multilocular}\end{array}\right\}\text{cysts; or,}$$

$$\text{Simple}\left\{\begin{array}{c}\text{unilocular}\\ \text{or}\\ \text{multilocular}\end{array}\right\}\left\{\begin{array}{c}\text{intracystic hemorrhagic}\\ \text{or}\\ \text{extracystic hemorrhagic}\end{array}\right\}\text{cysts.}$$

CYSTADENOMAS

This group contains all those cysts which are lined by columnar (Figs. 145, 146, 148, 152, 153, and 154) or cuboid epithelium and which contain a highly albuminous, pseudomucinous, or gelatinous material. Cysts with these characteristics may be described as simple cystadenomas. They may be single or multiple. They may have hemorrhage into the cavity of the cyst (Fig. 148) or into the wall. The epithelial lining may be hyperplastic and thrown into folds or papillomas (Figs. 152, 153, 154, and 156), which have connective-tissue pedicles and are covered with epithelium which is continuous with that which lines the cyst. Such papillomatous neoplasms may be intracystic (Figs. 152, 153, and 154) or extracystic (Fig. 155). The extracystic papillomas are the result of destruction of the wall of the cyst and growth into the abdominal cavity (Fig. 155). The epithelium of ovarian cyst adenomas, like that of the breast, does not always produce

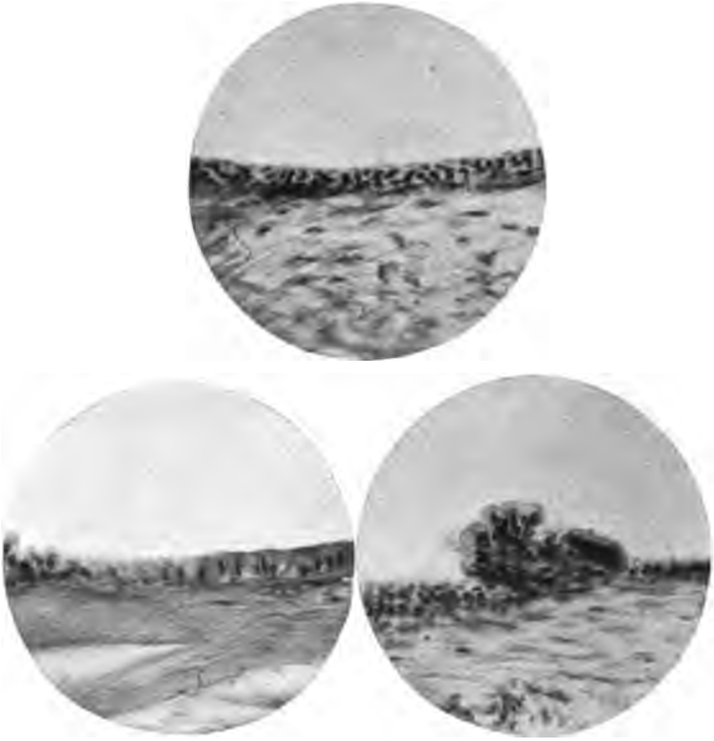


Fig. 147.—Photomicrographs of the lining epithelium of one small cyst.

intracystic papillomas. On the contrary, it may grow into the underlying tissue and present itself as a true adenocarcinoma, thus forming a solid mass in the walls of cysts (Fig. 157). The essential

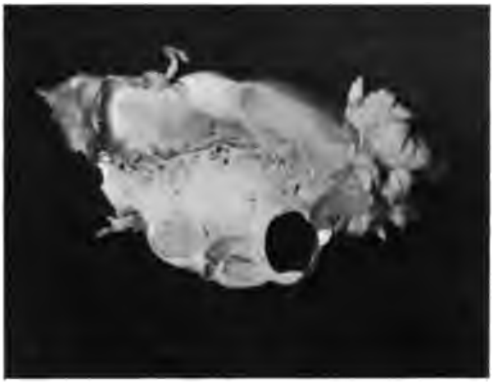


Fig. 148.—Small hemorrhagic ovarian cystadenoma.

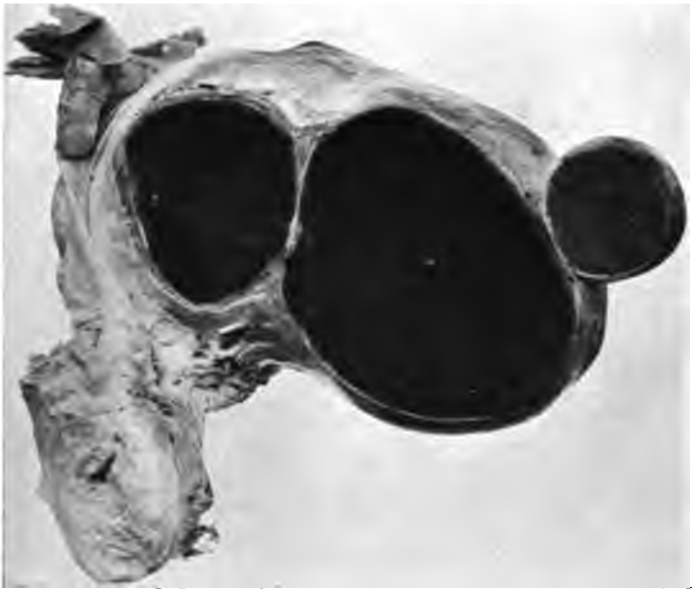


Fig. 149.—Large hemorrhagic cysts ("tarry cysts"). Epithelium not demonstrable.

characteristics may be presented in the following descriptive terms:

$$\left.\begin{array}{c}\text{Unilocular}\\\text{or}\\\text{multilocular}\end{array}\right\}\ \left.\begin{array}{l}\text{simple or intra-}\\\text{or extracystic}\\\text{hemorrhagic}\end{array}\right\}\ \left\{\begin{array}{l}\text{Intracystic or}\\\text{extracystic}\\\text{papillomatous}\\\text{or carcinomatous}\end{array}\right\}\ \text{cystadenoma.}$$

HEMORRHAGIC CYSTS

The line of demarcation between a normal corpus luteum and a so-called corpus luteum cyst is just as indefinite as that

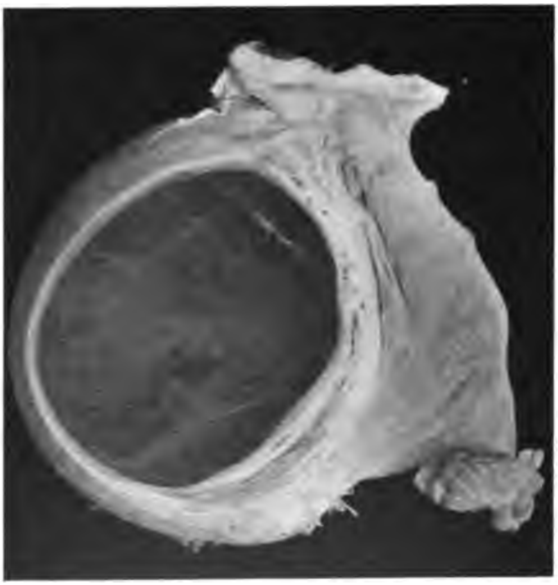


Fig. 150.—Large degenerating ovarian cyst. Epithelial lining is destroyed; origin is therefore unknown.

between a Graafian follicle and a simple cyst. In practice both the surgeon and the pathologist are prone to call any hemorrhagic cyst a corpus luteum cyst which is smaller than a fist, or perhaps a child's head. The limits of size of a corpus luteum are unknown.

In view of the fact that our knowledge on the subject is indefinite, it seems to the writers that such a definite term as "corpus luteum cyst" is not a legitimate one. It allows the surgeon to unconsciously confuse those who accept his operative reports. The diagnosis is one for the microscope, and should be made only after lutein cells have been demonstrated in the border.

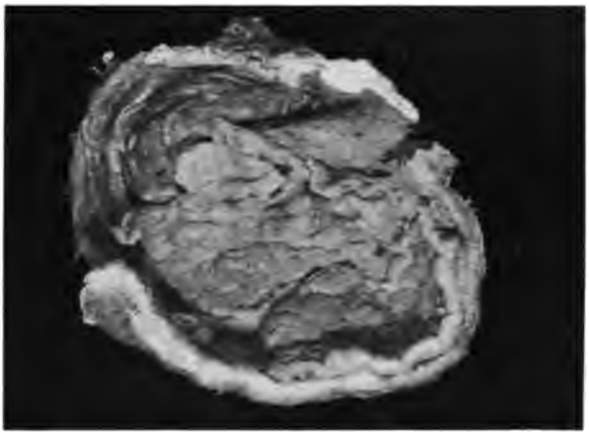


Fig. 151.—Interior of an ovarian abscess.

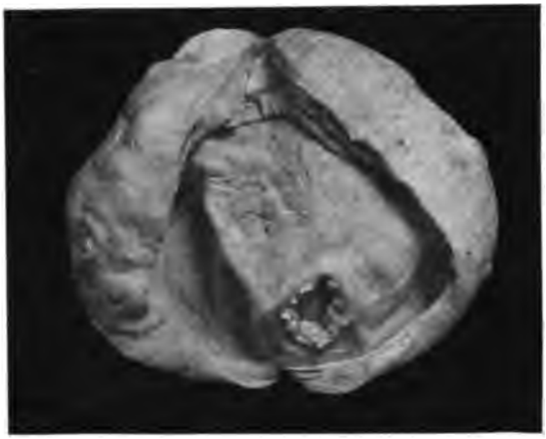


Fig. 152.—Intracystic papillary ovarian cystadenoma.

Hemorrhagic cysts of the ovary have different characteristics. They may be hemorrhagic simple cysts (Figs. 143 and 144), hemorrhagic cystadenomas (Fig. 148), or large corpora lutea (Fig. 150). The differentiation between these grossly has been impossible in the writers' experience.

The clinical significance of all ovarian cysts, *i.e.*, the simple cysts, the simple papillary and carcinomatous cystadenomas, and the hemorrhagic cysts, depends on the life-history of their lining epithelium. Ordinarily the Graafian follicle should run its natural course, discharge its ovum, and recede with the formation of a corpus luteum. In case the Graafian follicle continues to develop instead of rupturing and forming a corpus luteum, a so-called simple cyst, occurs with the characteristics described above.

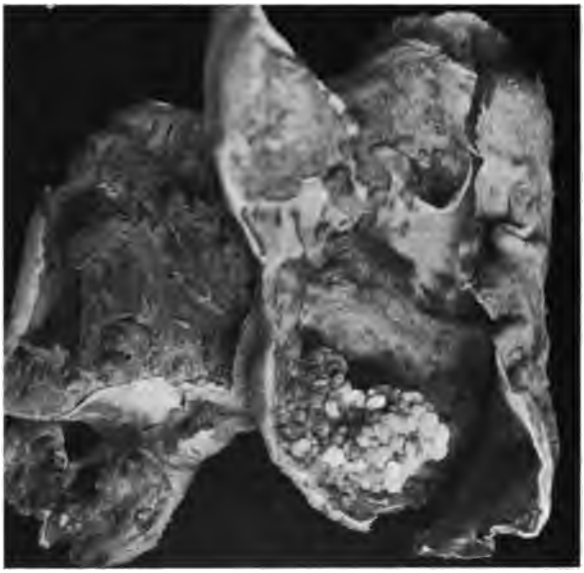


Fig. 153.—Intracystic papillary ovarian cystadenoma.

Experience demonstrates that malignant ovarian cysts do not possess epithelium of the type which one finds to be the dominating type in simple cysts. Their morphologic sign of malignancy is the irregular hyperplasia of the columnar epithelium of the cystadenomas. In the writers' experience, all carcinomatous and papillomatous cysts have apparently originated from cystadenomas.

The question of the origin of the cystadenomas has been answered in literature by hypotheses rather than proof. Pflüger's tubules, Wolffian tubules or rests, and Graafian follicles have all been held theoretically responsible. The writers believe there is only one fact which points toward at least one source of the cystadenomas.

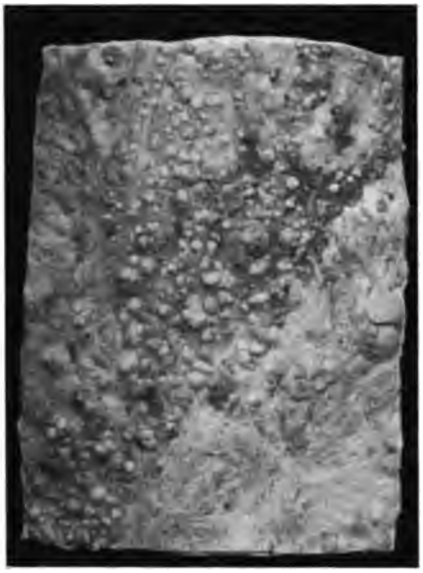


Fig. 154.—The inner surface of an intracystic papillary ovarian cystadenoma.

Cystadenomas in the ovary bear a certain resemblance to cystadenomas in the breast. This is especially true in the light of hyperplasia of the lining epithelium. In the case of the normal hyperplastic mammary epithelium one finds two distinct layers, the inner layer of which is absent in cystadenomas and carcinomas.* In ovarian cystadenomas and carcinomas the same phenomenon is true. During extensive hyperplasia the inner row disappears. The evidence which points to the occurrence of the same process in the ovary may be seen in the accompanying photographs (Figs. 158 and 159). The first picture (Fig. 158, *a*) presents the lining wall of a Graafian follicle, the second (Fig. 158, *b*) that of simple cysts. In the second (Fig. 158, *b*) the epithelium is similar to that of the Graafian follicle. In the third (Fig. 158, *c*) two types of epithelium are readily visible. The inner row (the row next to the lumen) consists of many layers of round or oval cells, which rest upon the outer columnar row. The fourth picture (Fig. 158, *d*) presents a cyst-wall lined by columnar epithelium.

---

* MacCarty, Trans. of the Southern Surgical and Gyn. Assn., 1910, Old Dominion Med. Jour., 1911, xii, pp. 189–198.

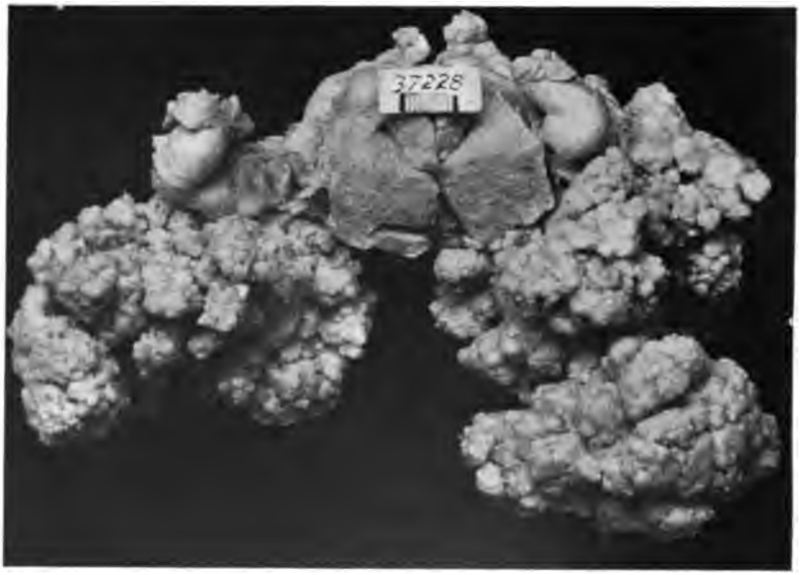


Fig. 155.—Extracystic papillary ovarian cystadenoma.

This series of specimens is very striking in view of the behavior of the mammary epithelium. It is especially interesting when associated with another case in this series (Fig. 147), which shows the lining of a single cyst, which presents three distinct features, *i. e.*, the many-layered epithelium of the Graafian follicle and simple cyst, the columnar epithelium of the cystadenoma, and the papilloma of the intracystic papillary cystadenoma.

These facts suggest a process—the stages of which have been

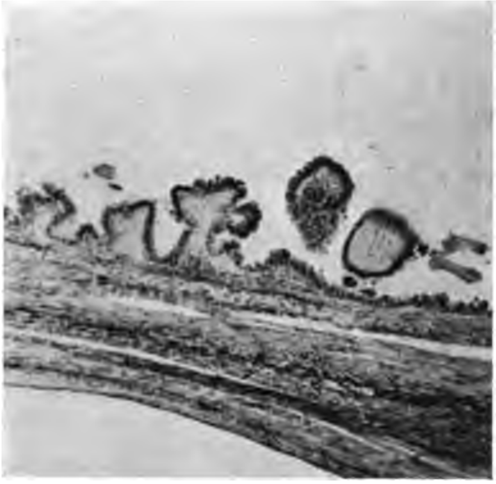


Fig. 156.—Low-power photomicrograph through the wall of a papillary ovarian cystadenoma.

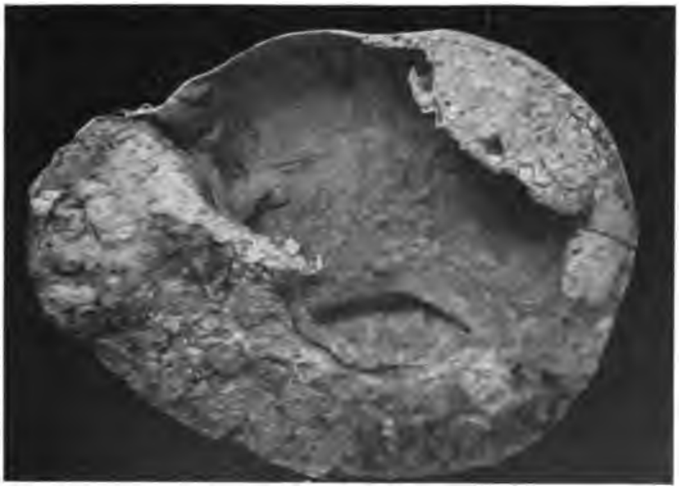


Fig. 157.—Carcinomatous ovarian cystadenoma.

termed entities. All unruptured follicles, most probably, do not pass through all stages, just as all cysts of the breast do not become cystadenomas. These observations do not interfere with the possibility of origin of cystadenomas from Pflüger's tubules, Wolffian tubules, or Wolffian rests.

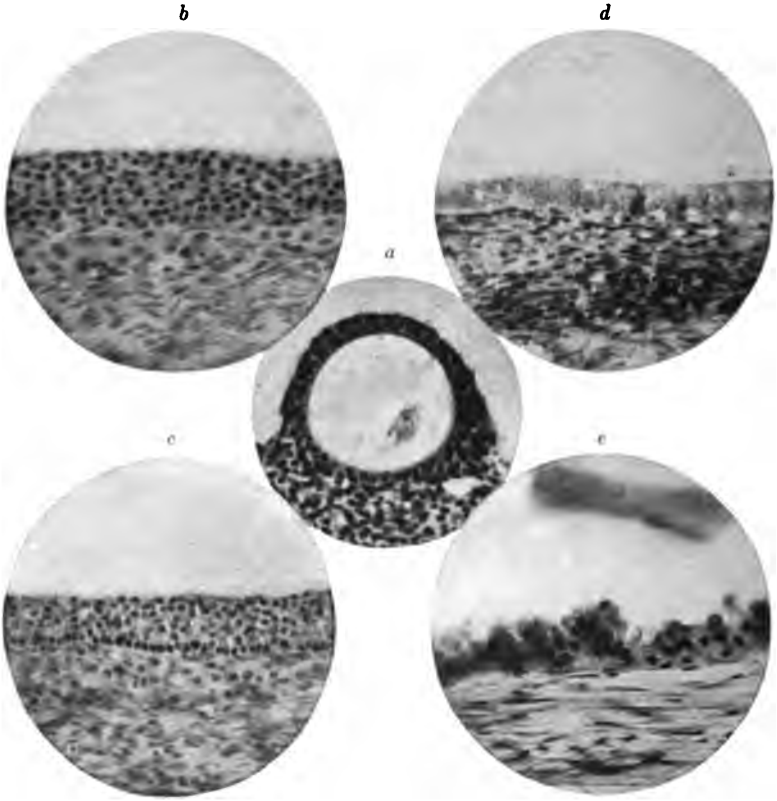


Fig. 158.—*a*. An ovum showing the morphologic character of the lining epithelium of a Graafian follicle; *b*, epithelium lining a Graafian follicle or small simple cyst; *c*, epithelium lining a simple cyst, showing also the basal layer of cuboid or columnar cells; *d*, columnar epithelium lining a cystadenoma; *e*, hyperplastic columnar epithelium lining a cystadenoma.

In view of these facts, certain clinical and operative questions arise:

1. When operative procedure consists of artificial rupture of a cyst without removal, what are the chances of rupturing a cystad-

enoma? This question may be answered by saying that small ovarian cystadenomas occur in a hemorrhagic or non-hemorrhagic state (Figs. 148, 145, 146), and that their differentiation from simple hemorrhagic or non-hemorrhagic cysts is determinable only by the microscope.

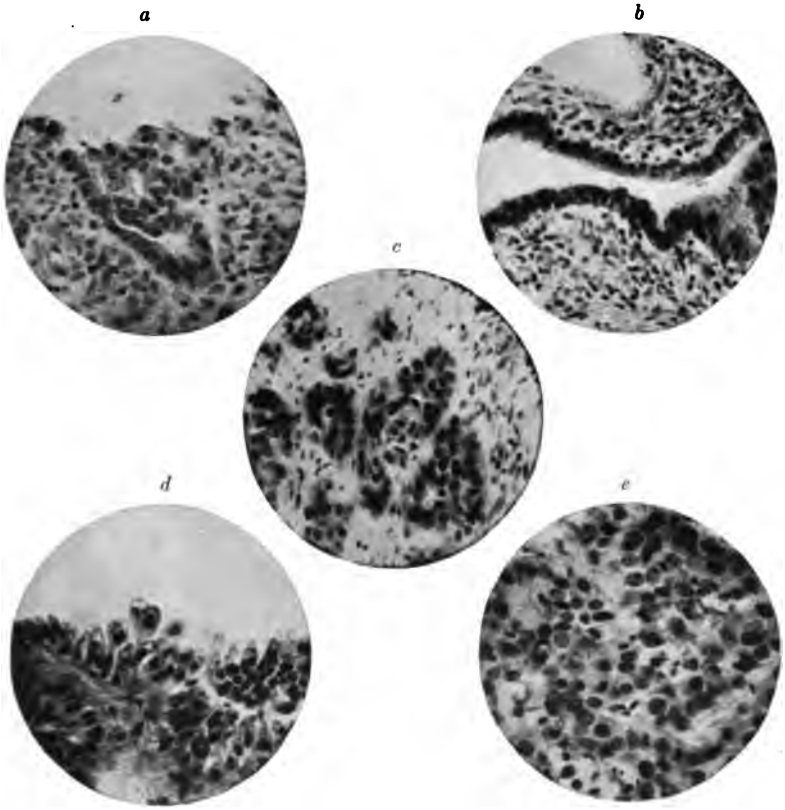


Fig. 159.—*a*, Epithelial invasion of the stroma in a carcinomatous cystadenoma; *b*, epithelial invasion of the stroma in a carcinomatous cystadenoma; *c*, *d*, *e*, irregular epithelial hyperplasia in a carcinomatous ovarian cystadenoma.

2. Would the artificial rupture of a small ovarian cystadenoma prevent further development? This is important, but is unanswerable at present. Experience teaches that large cystadenomas, however, certainly continue to develop after rupture.

3. In young individuals with cystic ovaries, which the surgeon ordinarily removes or punctures, would it not be more conserva-

tive to determine the exact microscopic nature of a portion of the cyst wall during operation? By so doing a simple cyst may be ruptured without destruction of an ovary, and cystadenomas will not be left in an attempt to conserve ovarian tissue.

Diagrammatic drawings through the walls of various types of ovarian cysts.

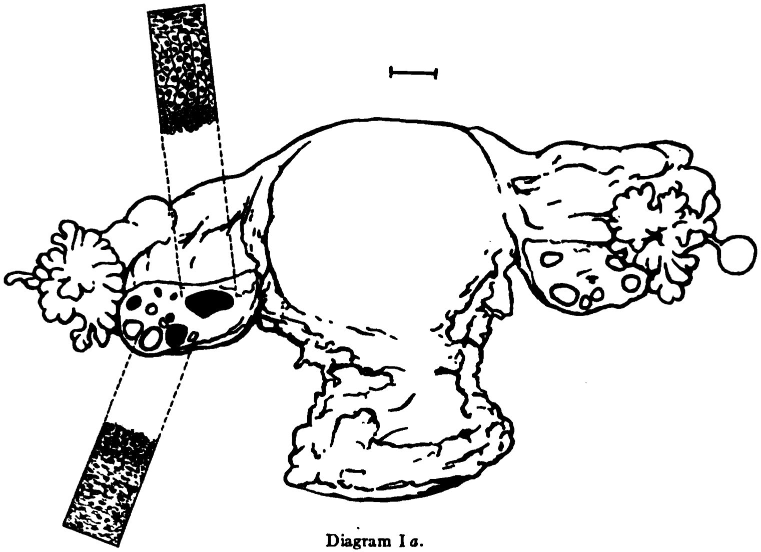


Diagram I *a*.

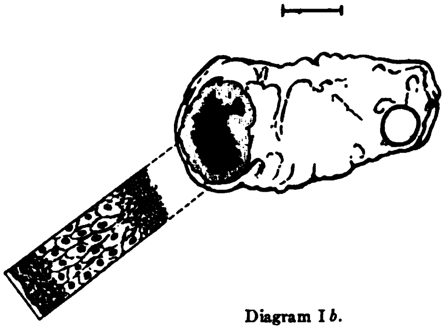


Diagram I *b*.

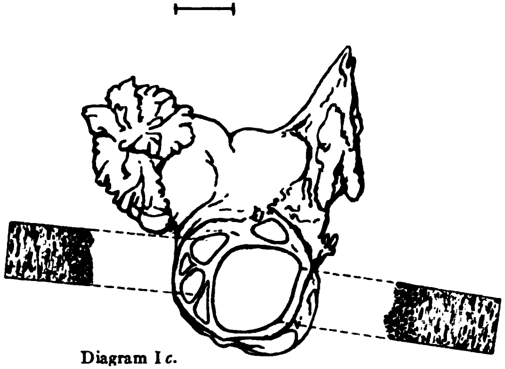


Diagram I *c*.

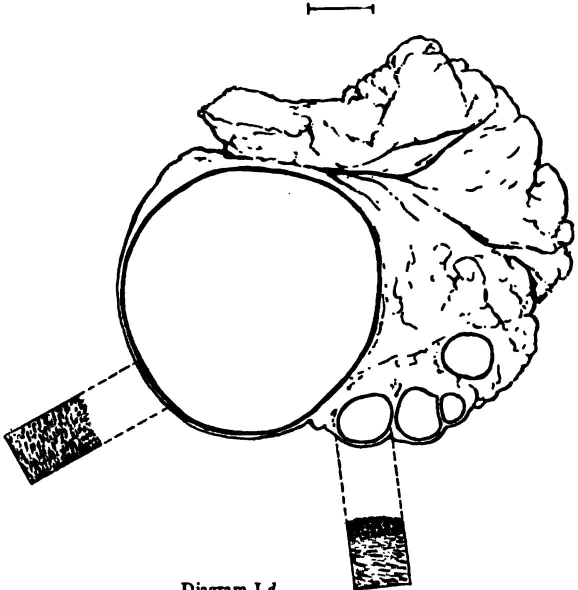


Diagram I *d*.

Diagram I.—*a*, "Normal" ovary containing Graafian follicles and corpora lutea; *b*, corpus luteum; *c*, simple ovarian cysts; *d*, simple ovarian cysts.

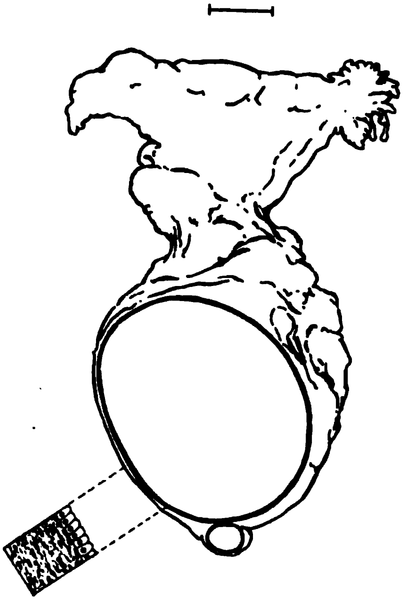


Diagram II *a*.

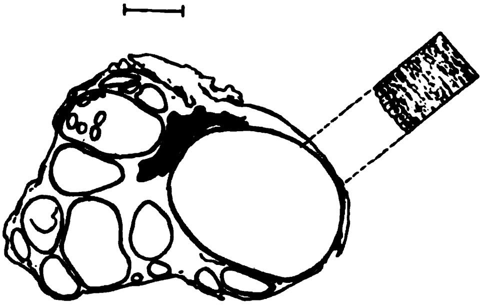


Diagram II *b*.

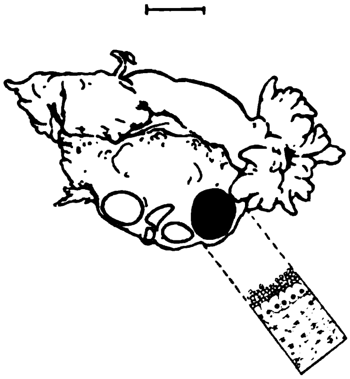


Diagram II *c*.

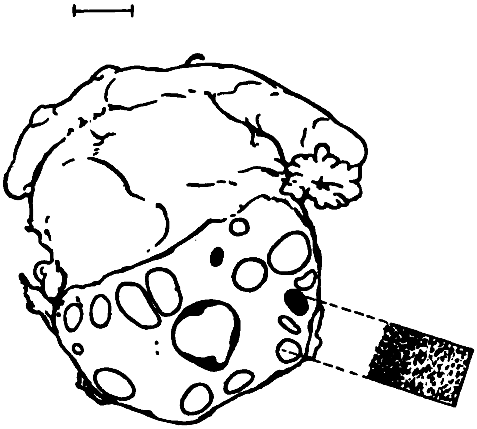


Diagram II *d*.

Diagram II.—*a*, Ovarian cystadenoma; *b*, extracystic hemorrhagic cystadenoma; *c*, intracystic hemorrhagic cystadenoma; *d*, intracystic hemorrhagic simple cysts.

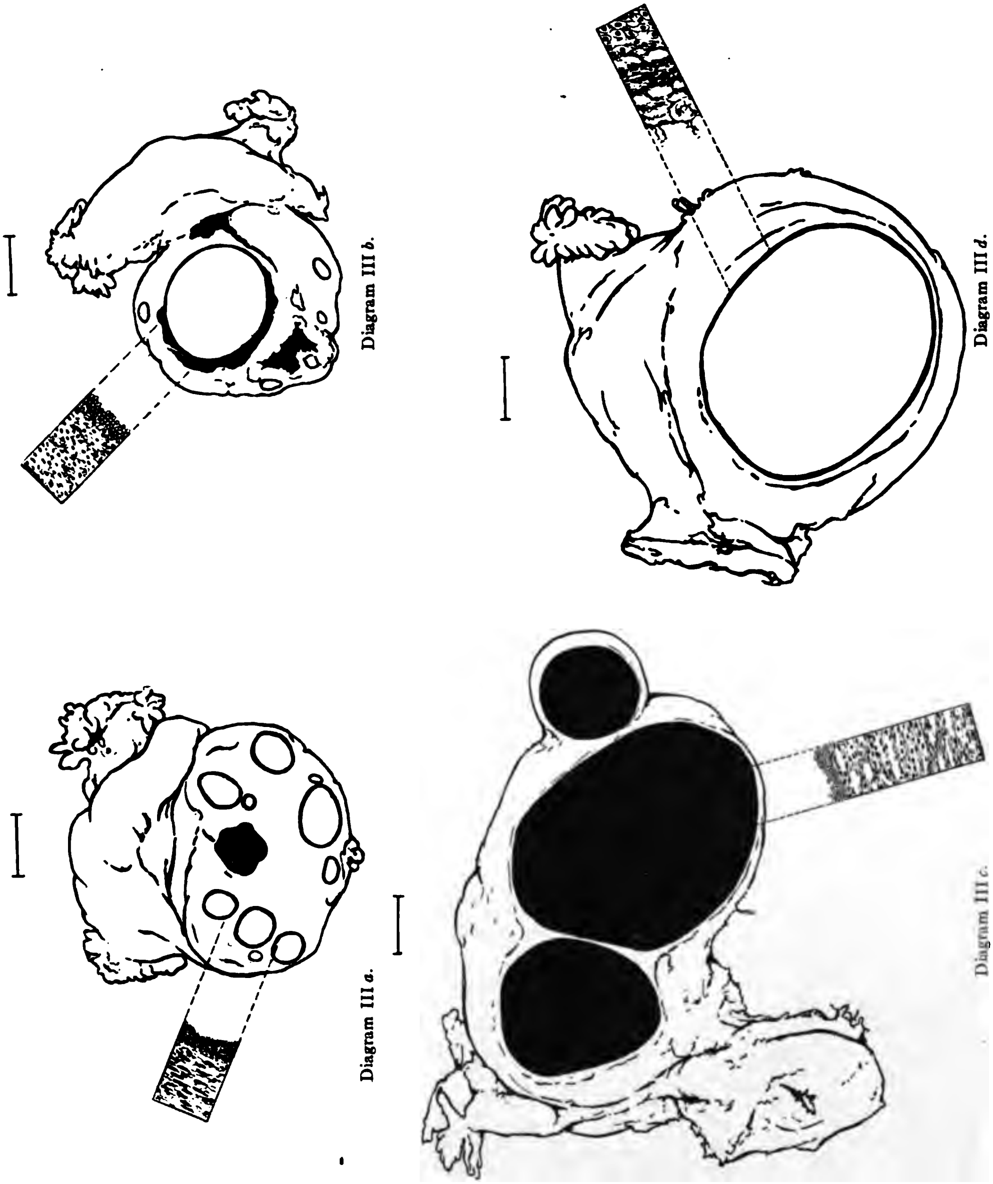


Diagram III.—*a*, Intracystic hemorrhagic simple cysts; *b*, extracystic hemorrhagic cysts (type unknown); *c*, intracystic hemorrhagic cysts (tarry cysts—origin unknown); *d*, large cyst with fibrinous contents (type of cyst unknown).

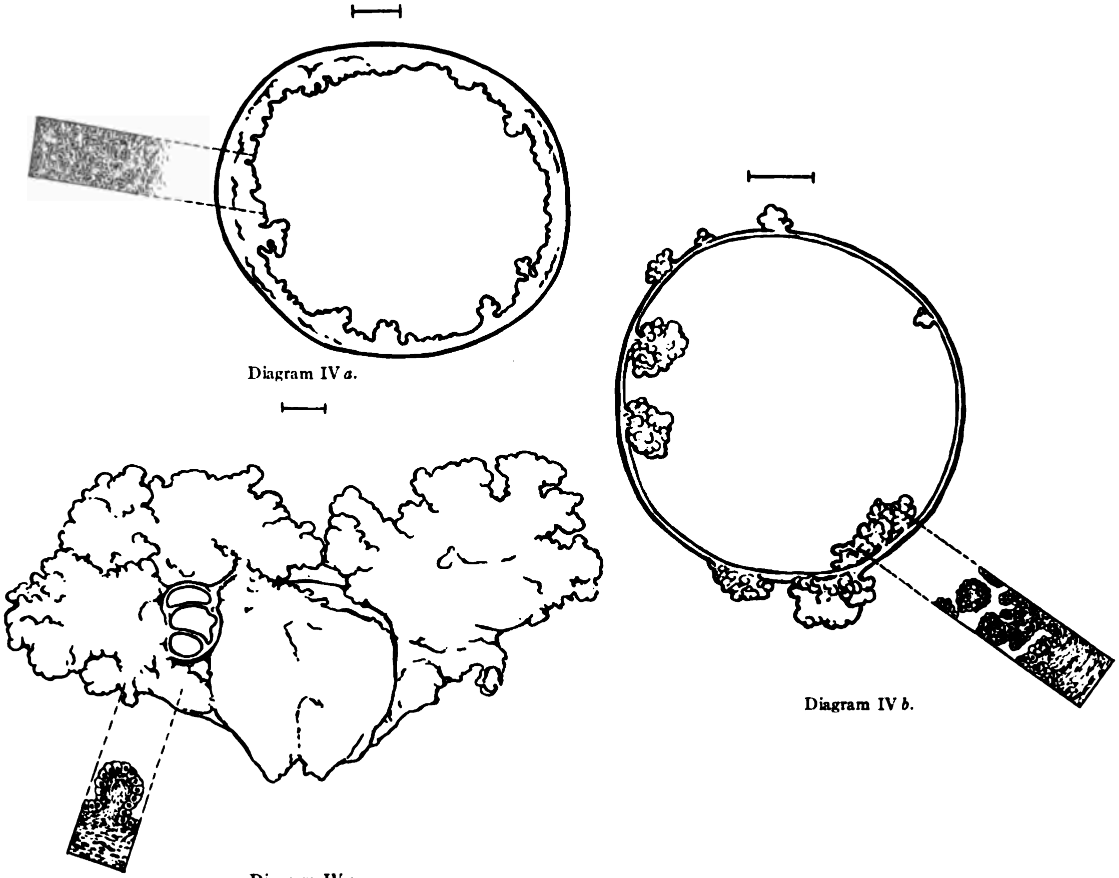


Diagram IV *a*.

Diagram IV *b*.

Diagram IV *c*.

Diagram IV.—*a*, Ovarian abscess; *b*, intracystic and extracystic papillary ovarian cystadenoma; *c*, bilateral extracystic papillary ovarian cystadenoma.

NOTES ON CARCINOMA OF THE UTERUS *

LEDA J. STACY

The text-books published between the years 1860 and 1875 scarcely mention the subject of cancer. In 1858 Wagner contributed a monograph on carcinoma to the literature, and the first clinical picture of carcinoma was described in Schräder's text-book in 1874. "Carcinoma was described early in the last century by pathologists, but it remained for Robin, in a paper published in 1855, to demonstrate that the disease had its commencement in epithelium. In 1865 Cornil also showed clearly the epithelial origin of the disease. In 1867 and again in 1872 Waldeyer showed conclusively that all cancers owe their development to a proliferation of epithelium" (Cullen). Since then the histology of cancer has become well established, but the etiology of the condition is the object of research in all countries at the present time.

All investigators state that cancer in general is increasing. Part of this increase is due to the more careful reporting of the cases, and to the fact that more people reach the cancer age than formerly. However, the statistics for England show that 1 in every 11 men and 1 in every 8 women over thirty-five years of age die of the disease, which is a greater death-rate for the same age period than occurs from tuberculosis. Reports from the Cancer Commission of the American Medical Association in 1909 give nearly one-half as many deaths from cancer as occurred from tuberculosis. In New York the mortality increased in proportion to the population 25.4 per cent. in ten years, from 1896 to 1906, while the tuberculosis rate decreased 4.9 per cent.

---

* Read before the Southern Minn. Med. Soc., Mankato, January 16, 1912. Reprinted from "Amer. Jour. of Obstet. and Dis. of Women and Children," 1912, vol. lxv, No. 6, pp. 946–952.

(Wainwright). The statistics of Minnesota show that about 1 in 17 of the deaths in 1908 were due to cancer.

Three factors are responsible for this mortality: (1) Ignorance on the part of the laity as to the early symptoms, the fact that pain is a late symptom and that the general health is not impaired, to the dread of cancer, and to the still prevalent belief that cancer cannot be cured. It is shown that from 94 to 97 per cent. of women with cancer of the cervix come to the surgeon too late to obtain a cure. (2) The failure of the physician to examine the patient, his inability to recognize the disease early, or his failure to give proper advice. (3) The cases which do not actually give rise to symptoms until too late for operation; this occasionally occurs.

The Commission on Cancer of the Medical Society of Pennsylvania during 1910 gives a very startling report made from data of 400 cases of cancer which had come to the surgeons for radical cure. In 3 per cent. of the patients with involvement of the breast, in 9 per cent. with involvement of the stomach, in 20 per cent. of uterine and 14 per cent. of ovarian involvement, no physical examination was made by the physician who first saw the case. Patients consult a physician to obtain relief from symptoms; they very seldom make an objection to a complete examination, and any such objection is soon withdrawn if its importance is explained. The complete examination should be made at the first consultation; if not, the chance for cure may be lost.

Welch says: "If the sum total of all cases of cancer in women be taken, the conclusion is that about one-fifth of all primary cancers are situated in the stomach, and somewhat less than one-third in the uterus." American statistics in general show that in 38.6 per cent. of the cases the disease is located in the stomach, while 27.68 per cent. are in the uterus, 15.78 per cent. in the breast, and 12.59 per cent. in the liver.

Cancer of the cervix is considered by most authorities as much more frequent than of the body of the uterus. In 182 cases reported by Cullen the disease occurred in the cervix in 81 per cent. and in the fundus in 19 per cent. In our series of 263 cases of cancer of the uterus (1900 to 1910 inclusive) the percentage in the body was higher than in the cervix—there were 58.18 per cent. in the body and 41.82 per cent. in the cervix.

Cancer of the cervix occurs more frequently in younger individuals, is more rapid in its course, and spreads more quickly to the surrounding tissues than to the body of the uterus. In our series of 110 cases of cancer of the cervix the average age was 46.13 years. There were 8 patients between twenty-five and thirty-five years of age, and 6 who were over sixty-five years of age. The largest percentage (37.2) was between forty-five and fifty-five years of age. In this series the duration of symptoms before coming to the surgeon was as follows: three months, or less than three months, 39.2 per cent.; six months, 13 per cent.; nine months, 12.9 per cent.; one year, 16.6 per cent.; two years, 8.7 per cent.; three years, 4.8 per cent.

In the report from Johns Hopkins Hospital of 412 cases of cancer of the cervix, in 61 per cent. the involvement was too extensive for more than palliative treatment. The cases at the Mayo Clinic during the ten years stated ran a little higher percentage, abdominal hysterectomy being done in 29 per cent. of the cases, vaginal hysterectomy in 39.1 per cent., a curet and cautery in 29 per cent., and amputation of the cervix in 3.6 per cent. The symptoms may be outlined as follows: (1) An irregular flow upon exertion, following strain or coitus, a douche, or a slight bloody discharge between menstrual periods. (2) A profuse flow, like a menstrual flow, but between the regular periods; or an increase in the regular flow. (3) Any sort of a bloody discharge, no matter how slight, after the menopause. (4) The appearance of a leukorrhea, when there has been none previously, or the onset of a foul, clear, watery, or blood-stained discharge. (5) Pain is a late symptom and usually means that the cancer has ceased to be a local disease, but has extended to the surrounding tissue and causes pressure on the nerves and blood-vessels. (6) Loss of weight and cachexia, which are also late symptoms.

In the series under discussion a bloody discharge was present in 76.5 per cent. of the cases; a watery discharge in 28.1 per cent.;

an odor to the discharge in 27.2 per cent., hemorrhage in 31.8 per cent. Pain occurred in 54.5 per cent., and was present for less than three months in 32.7 per cent. of patients before they came for consultation. Loss of weight was noted in 31.8 per cent. of the cases, with no loss mentioned in 33.6 per cent.

The physical examination, if made early, will reveal a hard, irregular cervix, or a hard, gristle-like "feel" will be noted just within the cervix. Later, an ulcer with a hard base and a friable surface, bleeding upon examination, may be found. If examination be made at a still later stage, a friable, cauliflower growth involving the entire cervix and probably extending onto the vaginal mucosa will be noted. Following an examination at this stage a hemorrhage may occur in addition to the constant bloody and watery discharge.

If the cancer be in the cervix above the os, the disease may be overlooked during the early stage. During examination the finger can usually be inserted through the os and comes in contact with the irregular and friable bleeding mass just inside the canal. With any of these findings and a history of irregular intermenstrual bleeding, time should not be lost in arriving at a definite diagnosis, and the patient given the proper advice and made to understand the importance of immediate attention.

In the 110 patients in our series menstruation was still regular in 30 per cent. and irregular in 35.4 per cent., and the menopause passed in 34.6 per cent. The average duration of irregularity was eleven months. Ninety-six and three-tenths per cent. of the women were married and 85.4 per cent. had been pregnant. Fibroids were present in 7.9 per cent. of the cases. There was a family history of malignancy in 6 cases. One patient had cancer of the breast as well as cancer of the cervix when she came under observation. One had been operated on for cancer of the breast two years before coming for the pelvic condition. Seven patients had had previous pelvic operations.

Cancer of the body of the uterus comes later in life, grows more slowly, remains a local disease for a longer period, and has a higher percentage of cures following operation. Cancer of the fundus produces the same symptoms as cancer of the cervix; the differentiation depends upon the physical examination. Given the history as stated above, if examination does not reveal any involvement of the cervix, the fundus should be carefully examined. The uterus is usually slightly enlarged and a little soft, with perhaps a general hardness of the cervix. Upon such findings the uterus should be cureted and all the scrapings examined microscopically. Even if no evidence of cancer be found, the diagnosis is not established because the area of the cancer might have been missed by the curet. We had one patient who had a curetment for diagnosis and no evidence of malignancy was discovered, but a year later she returned with a continuation of the symptoms; a hysterectomy was then done, and a cancer of the uterus found.

Occasionally a cervical polyp will cause an irregular bleeding. The polyp should be removed, the base cauterized, and a careful microscopic examination made. Following this operation the patient should be under close observation, and if the bleeding ceases, one can feel assured that the polyp was the cause of the symptoms. If the bleeding does not cease, curetment for diagnosis should follow.

In our series of 153 cases of cancer of the fundus of the uterus the average age was 50.8 years; the number having passed the menopause on the average nine years before coming to surgeon, 41.1 per cent.; regular menstruation, 17.1 per cent.; irregular menstruation, 20.2 per cent.; no mention of menstruation, 21.5 per cent. About 61.5 per cent. of the patients had been pregnant, and 12.3 per cent. of these had 6 or more than 6 children. Six patients had not been married. The duration of symptoms in these patients before seeking relief was over a longer period than in those with cancer of the cervix; 20.2 per cent. of the patients had symptoms for three months, 15.1 per cent. for six months, 12.4 per cent. for one year, 9.8 per cent. for two years, 5.8 per cent. for three years, 4.5 per cent. for four years, and 2.6 per cent. for five years. One patient had an occasional irregular flow and hemorrhages for eleven years, and one for nine years.

Fibroids existed in 14.3 per cent. of the cases of cancer of the fundus. In one case there were present a fibroid and a myxoma of the ovary, with cancer of the fundus. Ovarian tumors were present in 2 cases, and a polyp occurred in 2 cases. In this series 16 (10.4 per cent.) had had previous operation on pelvic organs.

Of the 153 cases in this group, vaginal hysterectomy was performed in 61, abdominal hysterectomy in 81, curetment and cautery in 10, and ligation of arteries in 1. Letters were sent to all these patients and 84 have been heard from. Of these, 52 are now living and in good health:

Number alive 1 year	9
Number alive 2 years	5
Number alive 3 years	6
Number alive 4 years	1
Number alive 5 years	8
Number alive 6 years	5
Number alive 7 years	6
Number alive 8 years	3
Number alive 9 years	4
Number alive 10 years	5

Three of the patients died in the hospital, one in diabetic coma, one of pneumonia. One patient lived nine years and two months and died of pneumonia, with no evidence of recurrence; another patient lived four years and died of pneumonia.

Number of patients who lived less than 1 year following operation	15
Number of patients who lived 1 year following operation	10
Number of patients who lived 3 years following operation	1
Number of patients who lived 4 years following operation	1
Number of patients who lived 8 years following operation	1
Number of patients who lived 9 years following operation	1

Replies were received from 64 of the 110 patients with cancer of the cervix. Of these:

Number alive 1 year	2
Number alive 2 years	6
Number alive 3 years	4
Number alive 5 years	2
Number alive 6 years	1
Number alive 7 years	2
Number alive 9 years	1
Number alive 10 years	1
Number alive 12 years	11

Two patients died in the hospital.

Number of patients who lived less than 1 year	12
Number of patients who lived 1 year	25
Number of patients who lived 2 years	3
Number of patients who lived 4 years	1
No time mentioned	1

CONCLUSIONS

1. Cancer in its early stage is removable and hence curable.

2. Cancer of the uterus usually gives symptoms in that early, operable stage.

3. Most of the deaths from cancer are due to delay, either on the part of the patient or of the physician first consulted, and are, therefore, unnecessary.

4. The laity should be made to realize that any irregular flow, a constant bloody discharge, or a watery discharge is not due to "change of life," but, in practically all cases, means malignancy.

5. The laity must be taught that cancer is curable if operated on early, *i.e.*, while still a local disease.

6. Physicians should make an early and careful examination and give the proper advice without delay.

REFERENCES

Wagner: "Der Gebärmutterkrebs," Leipzig, 1858.
Schräder: "Carcinoma," 1874.
Cullen: "Cancer of the Uterus," 1900; also "Johns Hopkins Hospital Reports," 1897, vol. vi.
"Reports from the Cancer Commission of the Amer. Med. Assoc.," "Jour. Amer. Med. Assoc.," 1908, vol. xlvii, pp. 1868, 1869.
Wainwright: "Penna. Med. Jour.," 1909, vol. xii, pp. 924–930.
"Commission on Cancer of Medical Society of Pennsylvania (Wainwright)," "New York Med. Jour.," December 9, 1911.
Welch: "Pepper's System of Medicine," vol. ii, p. 533.
"Report from Johns Hopkins Hospital of 412 Cases of Carcinoma of the Cervix (Sampson)," "Jour. Amer. Med. Assoc.," May 20, 1905, pp. 1586–1593.

CESAREAN SECTION AND CESAREAN-PORRO OPERATION *

REPORT OF 12 CASES

E. S. JUDD

Because of the high mortality the cesarean operation was, for many years, considered a procedure of absolutely the last resort. The greatly diminished risk in recent years has been brought about, as in all branches of surgery, by the development of aseptic technic, and the cesarean operation now has a broad field of election. The present mortality is not due to the operation itself, but to the condition in which the patient is found.

In considering the best method of delivery to pursue in any atypical case of labor, we should select a method which offers the least danger to the life and health of the mother and yet the greatest safety for the child.

In enumerating the chief indications for cesarean section we have first to consider the contracted and deformed pelvis. It was formerly believed by most obstetricians that cesarean section should be chosen when the true conjugate was 7 cm. or less, but with the added safety of improved technic it is generally believed now that this method should be chosen if this dimension is 8 cm. or less. It is not so important to determine the exact dimensions as it is to know the disproportion between the pelvic passage and the head of the fetus which must pass through it. The child's head may be large and immoldable because of thick cranial bones and unable to pass through an ordinary pelvis.

Neoplasms of any of the pelvic viscera may interfere with the

---

*Read before the Southern Minn. Medical Association, Mankato, December 3, 1912. Reprinted from "St. Paul Med. Jour.," February, 1913, pp. 70–78.

natural labor, and would be a reason for selecting the cesarean method, since the tumors may be removed at the same time. The operation would seem to be indicated and chosen in any case in preference to craniotomy if it be known that the child is alive, and, under favorable circumstances, would often be selected in preference to high forceps and podalic version.

Many observers who have had large experience feel that it is the best and safest procedure in central placenta prævia. Deaver[1] believes that it is the method of choice in practically all cases of placenta prævia. Davis and Markoe[2] hold that, while the mortality is high in cases of eclampsia, it is frequently the easiest and quickest way to empty the uterus, and for that reason is more favorable for both mother and child.

If we have a choice as to the time to operate, it is better to wait until labor has begun. It is unnecessary to wait for dilatation of the cervix and it is more desirable that the sac be not ruptured. The effects alone of uncomplicated labor produce a toxemia, so that a prolonged labor in itself is a contraindication to the operation. In a clean case there will be little or no mortality if the operation be done just before labor or during the early hours of labor. Each hour adds considerably to the risk though the first twelve hours are safe unless the labor has been unusually hard.

While the cesarean operation is much safer and simpler in recent years because of the improvements in technic it should not be undertaken when any other method is possible unless the surroundings permit a proper asepsis. One of the principal contraindications is the slightest suspicion of uterine infection. It will sometimes be necessary to do the operation in the presence of infection, but this will add considerably to the morbidity and mortality. The operation is much less favorable if there have been repeated vaginal examinations and especially if there have been many attempts at delivery through the vagina.

The question as to whether the operation is to be a cesarean delivery and the wound in the uterus closed or whether the uterus should be removed at the same time will depend on several factors, each case being considered individually. Ordinarily, if it be necessary to operate on a case when there is known infection in the uterus, it will be safer to do a hysterectomy at the same time, as extension of the infection to the peritoneum will be less liable to occur.

Uncontrollable hemorrhage is said to be a reason for removing the uterus. In none of our cases, however, has the hemorrhage been severe enough to indicate this procedure.

In case there are multiple fibroids, coincident removal of the uterus is often advisable, though Newell[3] believes that cesarean section should be done first and hysterectomy at some future time. Several of our cases have come to operation at full term with a large, hard cancer of the cervix. This, of course, necessitates removal of the entire uterus. Ordinarily, where it is advisable to remove the uterus, it is best to deliver the child and the placenta through the ordinary incision in the uterus. This permits the uterus to contract so that it is more easily removed and with less loss of blood to the patient.

There are several methods of performing the so-called cesarean section. The vaginal method has reached great favor, especially in Germany. It is accomplished through an incision in the anterior wall of the cervix after the bladder and peritoneum have been stripped back and the cervix pulled down. This method seems especially useful in eclampsia, but cannot be used in cases of abnormal relationships or neoplasms. The abdominal extraperitoneal cesarean section has recently been favorably spoken of by German surgeons. This method consists of a low abdominal incision through the muscles, bluntly stripping the peritoneum off from the distended bladder and anterior surface of the cervix and uterus. The child is delivered by forceps through an incision in the uterus at this point. Küster[4] claims that in this deep cervical extraperitoneal cesarean section it is immaterial whether or not there be infection so long as the peritoneum is not injured.

Until quite recently the operation most frequently employed in this country was the so-called Sänger operation. This consists of a long median abdominal incision, with delivery of the uterus onto the abdominal wall, constricting the cervix while the uterus is being emptied. This operation may be chosen especially when it is certain that the uterus should be removed at the same time. Davis and Markoe[2] have shown recently that a great deal of this procedure is ordinarily unnecessary, and if omitted, there will be much less reaction and shock than that seen in patients following the technic originally described by Sänger.

Another objection to the Sänger operation has been the adhesion of the abdominal incision to the incision in the uterus.

The technic as described by Davis and Markoe[1] consists in the same general and local preparation of the patient as for any abdominal operation, with no vaginal douches or attempts at vaginal cleansing. Vaginal examinations should be restricted and if possible the membranes should be intact. Twenty-five minims of ergot should be injected deep into the muscles a half-hour before the operation to guard against atony and undue hemorrhage. The patient is placed in a horizontal position and an incision 8 to 10 cm. long is made in the midline above the umbilicus. The abdominal wall is thin and stretched out and care must be used not to injure the viscera in making the incision. The intestines are packed off with one or two packs wet in salt solution. No attempt is made to lift the uterus out of the abdomen, but an assistant, by pressing on each side of the abdomen, holds the uterus up to the abdominal incision and continues this moderate pressure until the contents are delivered. The opening in the uterus is slightly larger than the abdominal incision and is made in the anterior wall, beginning below the fundus and extending downward toward the cervix. The hand is passed into the uterus between the uterine wall and the membranes, separating the latter from their attachment. The placenta often lies just beneath this incision, and, if so, may be separated, though, if the bleeding at this stage be too great, it is well to open directly through the placenta. The anterior thigh of the child is grasped and a breech extraction done. The child is handed to an assistant and the cord cut between two clamps. The uterus is grasped with the fingers and lifted up into the abdominal incision. The placenta and membranes are slowly stripped out. By this time the uterus will have contracted and in most instances there will be little if any bleeding. If the bleeding be excessive, a large gauze sponge or a towel may be packed into the uterine cavity. The wound in the uterus is closed by interrupted chromic catgut sutures, 6 to 10 in number, placed one-half inch apart, including all tissues except the mucosa. Over this is placed a running Lembert suture catching deeply. These interrupted sutures are buried under the peritoneum. The uterus is handled as little as possible and little attempt is made to clean out the abdominal cavity. The abdominal wound is closed in the ordinary manner. The uterus is allowed free play in the pelvis. When the patient is placed in bed the head of the bed is raised to favor drainage and the descent of the uterus into the pelvis. The after-treatment is the same as that for any laparotomy. The child is allowed to nurse in a few hours, and the mother may be gotten out of bed at the end of a week.

Markoe and Davis have reported 68,200 cases of labor in the Lying-in Hospital, New York. Of this number, 256 were cesarean sections, most of which were performed through a small, high incision. The mortality in these 256 cases was 14 per cent. to the mother, 12.74 per cent. to the child; 7.34 per cent. were stillborn. The mortality to the mother was due chiefly to eclampsia, general peritonitis, and pneumonia. Most of the patients with eclampsia were moribund when operated on, and the operation was done in an effort to save them. In each of the patients whose death was due to general peritonitis there had been a great deal of outside manipulation, and in many instances a number of attempts at delivery.

Many surgeons have discussed the advisability of making these patients sterile by resecting the tube at the time of operation. This would appear to be a question which should be decided by the individual patient. Many times women will object to this procedure, since they are anxious to have a family even though their children must be born by the cesarean method. A large number of cases are on record of the operation having been done repeatedly on the same woman.

St. Mary's Hospital is not provided with an obstetric clinic, and these patients are not ordinarily referred to the hospital.

CESAREAN SECTION AND PORRO-CESAREAN OPERATION

Case No.	Age	Date of Operation	Previous Pregnancies	Hours in Labor	Diagnosis	Indication	Operation	Result
74010	17	9-21-12	One miscarriage at three months	Forty hours' hard labor. Forcible dilatation	Small pelvis. No engagement	Small pelvis. Large head	Davis operation. Inert uterus	Live female child, 7½ pounds. Hard convalescence
65058	22	3-3-12	None	Thirty-six attempts with forceps failed	Contracted pelvis. No engagement	Large fetal head Small pelvis	Davis operation	Live female child, 7½ pounds
Mrs. A. D. V.	30	11-16-98	None	Fifty unsuccessful attempts by all methods	Moribund. Child dead a few hours	Marked shock. Attempt to save mother's life	Sänger operation	Patient died—ten hours, not recovering from shock
69314	33	6-15-12	3 pregnancies; first lived seven weeks; second and third lost —forced labor	Ten	Anteroposterior contraction	Contracted pelvis	Davis cesarean	Puerperal insanity. Nine-pound male child. Complete recovery
17589	30	3-8-12	None	Six	Deformed pelvis. Pathologically dislocated hips. Tuberculosis	Contracted pelvis. Old pathologic process in bones	Davis cesarean	7-pound male. Complete recovery
16354	48	3-14-12	None	Thirty attempts with forceps	Small pelvis	Contracted	Davis cesarean	6-pound female. Complete recovery
67545	31	5-7-12	7 children; 3 miscarriages	Labor off and on one week. No pain, no life felt for six days	Large, soft, movable carcinoma of cervix. Full term. Dead child	Carcinoma of cervix. Dead child	Davis cesarean	Dark colored fluid. Child dead some days. Immediate total hysterectomy. Recovery
62134	26	12-11-12	None	Thirty-six attempts with forceps	Small pelvis. No engagement	..	Davis cesarean	Complete recovery
Mrs. O. L.	25	6-29-99	2 stillborn	..	..	..	Porro-cesarean	Male child. Complete recovery
Mrs. W. V. LeB.	41	9-6-95	None	..	Eight and one-half months pregnant. Constant, severe; fibroid	Uterine fibroid	Porro-cesarean	Complete recovery
31848	43	6-8-10	1 miscarriage at six weeks, three years previously	Twenty-four, mild labor	Large, multiple uterine fibroid	..	Porro-cesarean	Complete recovery
23205	33	6-9-10	None	Mild, several days; 4 children; 1 miscarriage	Extensive carcinoma of cervix. Full-term pregnancy	..	Porro-cesarean	Died fourth day, suppression. Child lived

The 12 cases of cesarean section herewith reported might, therefore, be classed under the head of emergencies.

In this group of cases there were 8 cesarean operations (7 Davis, 1 Sänger) and 4 Porro-cesarean operations.

One of the 8 patients upon whom a Sänger cesarean section was performed was moribund, and died ten hours after the operation without rallying from the shock.

In another of the 8 cases of cesarean section (Davis) cancer of the cervix was the indication for the operation. The child had been dead for several days. The mother made an uneventful recovery.

In the group of 4 Porro-cesarean sections 1 case, a woman thirty-three years of age, had had 4 children and 1 miscarriage. She came to operation after having been in mild labor for several days. Examination revealed a full-term pregnancy and an extensive rigid cancer of the cervix. A Porro-cesarean operation was done and a healthy male child delivered. The mother died on the fourth day of acute nephritis. The autopsy was otherwise negative.

In all other instances the mother and child lived.

In this connection I will report a case of abdominal extra-uterine pregnancy at full term in a woman thirty years of age. This pregnancy had its origin in the left tube, and its blood-supply from the region of the uterus and sigmoid. The uterus was spread out over the wall of the sac which contained the child. The sac was surrounded by the transverse colon, stomach, and omentum. It contained mucosin, placenta, and a living child. The uterus, ovaries, and tubes were removed, and the large bleeding vessels in the sigmoid and base of the pelvis were ligated. One rubber tissue drain was left passing through the incision. The child, who had a deformed head and foot, died two hours after the operation. The mother recovered.

REFERENCES

1. Deaver: "Jour. Amer. Med. Assoc.," July 13, 1912, pp. 90–94.
2. Davis and Markoe: "Amer. Jour. Obst. and Dis. of Women and Children," 1910, vol. lxii, No. 6; also "Bull. of the Lying-in Hosp.," 1909, vol. v.
3. Newell: "Boston Med. and Surg. Jour.," September 19, 1912, pp. 383–389.
4. Küster: "Münch. med. Woch.," October 22, 1912, p. 2221.

SURGICAL TREATMENT OF PROLAPSE OF THE UTERUS AND WALLS OF THE VAGINA *

W. J. MAYO

A review of the records of St. Mary's Hospital from September 30, 1889, to September 1, 1912, shows that 629 women have been operated on for prolapse of the uterus. The patients coming to this hospital are largely from agricultural communities. The majority of these cases were of the more serious forms of this condition brought about by changes in the tissues, the result of repeated pregnancies, aided by physical exertion due to the occupation of the patients. In all of these patients the cervix presented itself at the vulvar orifice or protruded from the vagina with more or less of the vaginal wall. In many of the senile cases the entire uterus and a large portion of the bladder and rectum composed the constituents of the prolapse.

It is a curious fact that, while erosion and ulceration of the cervix are comparatively common, there were but two cases of malignancy recorded. This observation, however, cannot be accepted for its face value, since cases of malignant disease with prolapse may have been classified only as carcinoma of the uterus. The inference is interesting as showing that chronic irritation in a cervix exposed to the air and therefore dry may not have so great an influence in the causation of adenocarcinoma as might occur under moist conditions. Both the cases which occurred in our series were epitheliomas.

The cases can readily be classified into three groups:

The first includes those occurring during the child-bearing

---

*Reprinted from "Jour. Amer Med. Assoc.," October 19, 1912, vol. lix, pp. 1421–1424.

period, in which usually there is supravaginal hypertrophy of the cervix. This elongation may amount to from 3 to 7 inches. The vaginal face of the cervix protrudes from the vulva, but the body of the uterus maintains a position in the pelvis. The resulting cystocele and rectocele are seldom of extreme degree.

The second group includes those cases ordinarily seen during the age period of from forty-five to fifty-five years, when the child-bearing function is no longer of consequence. The uterus is still of fair size.

In the third or senile group of cases will be found elderly women in whom the uterus has undergone advanced atrophy. This organ, with the cystocele and rectocele, and often the entire vagina, lies outside of the body.

The cystocele is usually the most striking feature in these cases, especially those found in groups 2 and 3. It is a condition most difficult to remedy, and one which must be remedied to cure the patient. So long as hydrostatic pressure is brought to bear on the anterior vaginal wall by urine which remains below the pubic arch, I do not know of an operation which will relieve the patient. A permanent cure can be effected only by some method which will restore the bladder to a situation above the pubic arch.

The older operations for cystocele, those of Martin[1] and Stoltz,[2] for example, have long been abandoned because the scar tissues which were formed by narrowing the vagina failed to control this phase of the condition. The secret of cure in all these cases, therefore, lies in loosening up the bladder and by some means restoring it to its position in the upper pelvis and lower abdomen.

TREATMENT OF PROLAPSE DURING THE CHILD-BEARING PERIOD

Prolapse during the child-bearing period must be treated so as not to interfere with the child-bearing function. It should be remembered that many of these patients continue to bear children in spite of the prolapse.

We have found that high amputation of the cervix, not closer than one-half inch to the internal os, in connection with the external operation on the round ligaments, as originated by Alexander,[3] and with some type of perineal operation which elongates the posterior vaginal wall, will readily cure at least 96 per cent. of these patients. The cystocele is usually due to protrusion of the cervix, and since this protrusion is nearly always accompanied by supravaginal elongation of the cervix, the anterior vaginal wall, carrying with it the bladder, can be transplanted upward several inches by high amputation of the cervix. Occasionally, in amputating the cervix, we have loosened the tissues about the cervix posteriorly and laterally, exposing the uterosacral ligaments so that they could be shortened simultaneously.

Since the uterus in these cases is freely movable and comes into place readily, we prefer the external to the internal operation on the round ligament unless there be complications within the abdomen. The external operation gives quite as good results as the internal, and the patient will usually be more comfortable subsequently.

It is certainly true that an internal operation on the round ligament of any type is sometimes followed by chronic distress and pain, which is exceedingly rare following the external operation. The external operation is an excellent means of maintaining a movable uterus in position, yet it is an operation with but a small field of usefulness because uncomplicated retroversion seldom requires treatment.

We have complete records of the physical examination of many thousands of women. While the normal position of the uterus in the majority of women, perhaps 75 per cent., is more nearly anterior than posterior, it must be acknowledged that in at least 25 per cent. and at various ages retroposition exists. The condition will be found as often in the young girl as during the child-bearing period and after the menopause, and it is probable that retroposition of the uterus is even more common than these data would suggest. It is altogether probable that a uterus in retroposition is often lifted into the anterior position by the bimanual examination itself, before its position is definitely determined.

In performing operations in the upper abdomen, it has been our practice for some years to make a complete examination of the abdomen with the gloved hand, and we have found retroposition of the uterus to exist in at least 50 per cent. of the women examined. The evidence thus obtained, however, is robbed of some of its value, since these patients were under an anesthetic, which might influence relaxation of the uterine supports.

At one period the Alexander operation was practised indiscriminately by many surgeons. Fixing a movable retroversion for the cure of neurasthenic symptoms was an easy matter, but it did not cure the patient. We often forget that the brain and nervous system are as large and as heavy as the liver, and that the production of thought, sensations, etc., is the function of the central nervous system as much as the production of bile is one of the functions of the liver. Disturbance of the function of the brain and nervous system results in disturbed thoughts or sensations, which extend to all parts of the body. I have no sympathy with the view so often advanced that neurasthenia, neuroses, etc., always depend on physical causes independent of the brain and nervous system, just as though the nervous system had no right to have functional disturbances.

When it is considered that a large percentage of women have retroposition of the uterus, and that about 22 per cent. have a markedly movable kidney, it can be seen how little chance the neurasthenic has to escape an operation if the mere presence of such conditions is taken as evidence. As much also may be said of prolapse of the stomach and colon.

The external operation was also applied in a large number of cases of adherent retroversions and in those in which the symptoms were the result of inflammation of the ovaries and tubes, rather than the result of the position of the uterus. All these causes have led to the abandonment of an operation which gives definite and valuable results when properly performed on patients needing it.

On a number of occasions I have heard surgeons say that the permanence of an operation on the round ligaments depended on whether or not there were to be future pregnancies. It should not be forgotten that the round ligaments are non-striated muscle-fibers and part of the wall of the uterus itself, which has been projected forward to the spine of the pubes. The round ligaments undergo hypertrophy during pregnancy and involution following pregnancy. We have not found that repeated pregnancies have influenced the ultimate results in these cases. It has been a noticeable fact that in cases of prolapse during the child-bearing period the round ligaments are unusually well developed.

The external operation on the round ligaments has been performed in our clinic about as it was done by its originator; that is, an oblique incision, 2½ inches in length, is first made, ending over the spine of the pubes. The superficial layer of the superficial fascia is divided and the hemorrhage carefully checked to prevent staining the field. Opening the deep layer of the fascia exposes the pillars of the ring and the intercolumnar fascia. The intercolumnar fascia is separated with a pair of forceps, and a two-pronged blunt retractor is introduced into the lower angle of the wound. Traction is then made downward in such manner as to draw on the attachments of the round ligament to the spine of the pubis; this will ordinarily draw about ¾ inch of the cord, which will be recognized readily by its pinkish color, out of the canal. It must be remembered that the only part of the ligament which, when shortened, will affect the uterus is that which lies within the peritoneal investment. I have known the cord to be shortened without affecting the position of the uterus because the portion shortened lay only within the canal itself and did not draw on the uterus at all.

The perineal restoration which completes the combined operation for prolapse in the child-bearing period should be based on principles which will be referred to later.

TREATMENT OF PROLAPSE DURING MIDDLE AGE

The operation which we have used with great satisfaction in this group of cases, in which marked cystocele occurs, and in which the uterus is not atrophic, is the Watkins[4]-Wertheim[5] operation. While we have performed the operation for years, I think we have done it more satisfactorily since using the technic of Frankenthal.[6] The principles of the Watkins-Wertheim operation are correct, inasmuch as the bladder is first separated from the vagina and then from the anterior wall of the uterus, thus restoring the bladder to the abdominal cavity and drawing the fundus of the uterus forward into a complete anteversion with suture to the anterior vaginal wall, so that the bladder will lie within the abdominal cavity on the posterior wall of the uterus. When the bladder fills with urine it exerts upward traction instead of downward pressure. Since in many of these cases the prolapse began in the child-bearing period, and supravaginal elongation of the cervix is present, amputation of the cervix may be necessary, as it may be too long to lie in the hollow of the sacrum without flexion. If the Watkins-Wertheim operation be done during the child-bearing period, which is not often necessary, the Fallopian tubes must be separated from the uterus. If the uterus be not sufficiently large, that is, approximately near the normal size, this operation will fail.

We have had two cases of our own and have reoperated in three others in which an atrophic uterus subsequently not only failed to hold the bladder up, but was forced entirely out of the body. These cases were cured by the vaginopelvic fixation method as described hereafter. In some cases in which the cystocele was not so prominent a feature, we followed the plan of making a partial instead of a complete separation of the bladder from the uterus and attaching the anterior wall of the vagina to the uterus beneath the bladder, much as was done in the Mackenrodt[7] method of vaginal fixation for cure of the retroversion.

TREATMENT OF PROLAPSE IN ELDERLY WOMEN

The most generally useful operation for prolapse of the uterus in all types of cases beyond the child-bearing period is one which we have practised for about eighteen years and for want of a better name have called the "vaginopelvic fixation operation." It is especially applicable to those patients with a small uterus in whom the Watkins-Wertheim method cannot be applied and in all cases in which there is disease of the uterus which requires hysterectomy, or coincident disease of the ovaries and tubes. It is applicable, however, in all cases in which the Watkins-Wertheim operation can be used, and as a rule we prefer it in those cases requiring amputation of the cervix in connection with the Watkins-Wertheim operation. In our experience the patients have been more comfortable after this method.

The principles on which this operation depends are very simple. The vaginal wall with its attachments to the cervix lies outside of the body. By removal of the uterus, and usually of the ovaries and tubes, the round and broad ligaments can be secured high in the pelvic cavity and that part of the vaginal wall which was attached to the cervix outside the body is fixed to the round and broad ligament stumps inside the pelvis.

Failures have been extremely rare following vaginal fixation. The few failures which occurred were due to lack of care in making the fixation of the wall of the vagina to the stumps of the round and broad ligaments. The vaginal wall should be made to surround the stumps in such a manner as to furnish broad areas for union. Hysterectomy without such firm attachments only makes conditions worse, since the entire vagina prolapses subsequently, a condition which is exceedingly difficult to rectify. For the relief of complete prolapse of the vaginal walls following hysterectomy we have practised two methods. In the very old patient, when there was no object in saving the vagina, we removed it, allowing the bladder and rectum to come in contact. Vaginectomy is easy of accomplishment and a number of these elderly patients were promptly relieved of great distress by this means. When it is an object to save the vagina, as it is in most instances, vaginal fixation from above is practised and the vagina is attached to the round and broad ligaments through an abdominal incision. Or, if the original hysterectomy was supravaginal, we implanted the stump of the cervix in the muscles of the abdominal wall.

Kocher[8] has developed an operation which marsupializes the entire body of the uterus. The abdomen is opened in the median line, the uterus is drawn up, and the peritoneum drawn about the cervix, the abdominal walls and aponeurosis being made to grasp the uterus just above the cervix. The fundus of the uterus is then implanted so that it can be felt as a rounded tumor just beneath the skin. If the patient be in the child-bearing period, the tubes are disconnected from the uterus. Kocher has practised this operation for a number of years with great satisfaction. Two excellent modifications of this method have been produced by Crile[9] and Eastman.[10]

We have used the Kocher method on a number of occasions in two groups of cases: The first includes those in which prolapse existed and it was necessary to perform an abdominal operation for another purpose; the second group comprises the occasional cases in which a prolapse has existed for years, with thinning of the vaginal walls, making them parchment-like. This condition occurs only in the senile patient, and is usually associated with atrophy of the round and broad ligaments as well as of the uterus and vagina. The contraindication to the Kocher method is a short vagina.

Few organs in the body have been so much written about as the female perineum, which shows that a certain amount of dissatisfaction has existed with methods in use for its repair. In the early nineties I found a little book written by one of Tait's assistants, on "Tait's Flap-splitting Perineal Operation." It was curious to observe how this master surgeon anticipated the modern operation for the perineal repair. The Tait operation,[11] which has been generally condemned, was long called the "skin-perineum operation," because its principles were not understood. Much of this misunderstanding grew out of personal antagonism to its brilliant but eccentric originator. Tait was the father of modern abdominal surgery. Tait in England, Péan in France, and Price in America led the contest which placed surgery of the abdomen on a sound basis.

Tait's perineal operation had two important principles: First, it uncovered the muscles and structures, which had been separated, so that they might be accurately sutured together. Previous to

Tait's time the essential features of perineal operations were "bat wings," "butterfly," and other methods of removing mucous membrane. The form of the denudation is essential, as it necessitates grasping and bringing together the deeper structures of the perineum to close the denudations. Tait lifted the mucosa from the body of the perineum by careful separation at the mucocutaneous line, keeping inside the opening of Bartholin's glands. Many thick and painful perineums have been caused by dividing Bartholin's duct and by changes engendered thereby in the gland itself. Tait opened the perineum as one would open the abdomen in order to gain access to the parts to be repaired.

The second principle is one which I believe has not been generally recognized. The mucosa is lifted well off at each angle, but the dissection is not made deep in the midline. The apex or crest of the rectocele is then pushed upward and held inside the vagina; this traction draws on the torn fibers of the external and internal sphincters of the rectum. In closing, the lateral muscular structures were brought together and united with the torn sphincter fibers, restoring proper direction to the anal canal. This upward and inward traction of the crest of the rectocele also elongates the posterior vaginal wall. Tait carefully avoided the mucous membrane and skin in suturing and thereby avoided infection and pain.

Those interested in the type of perineal operation which deals with the muscular and fascial structures will find two articles of great value, one by Harris[12] on the transverse perineal muscles, and one by Hill[13] dealing with those muscles which are derived from the levator ani. The modern perineal operation exposes and sutures the perineal muscles and fascias with as much anatomic accuracy as would be developed in an operation for inguinal hernia.

Curiously enough, the worst type of rectocele may not be associated with prolapse, but exists as a true rectal hernia through the perineal body in which a circular opening with well-defined margins will be found just above the external sphincter. The sac lined with mucosa may be the size of an egg or an orange as it projects from the vagina. This condition is best corrected by separating the rectal structures from the posterior vaginal wall through the perineum in the usual manner. The sac is then drawn out through the anal orifice, after the sphincter has been thoroughly stretched. Following its extrusion it is caught in a clamp and cut away.

With a running suture of catgut the mucosa is closed and the suture line left protruding from the anus until it retracts. The method of suturing the mucosa is similar to the Pilcher[14] hemorrhoidal operation. After disposing of the rectal mucosa, the ordinary perineum is made as already explained. This method was first described by Noble,[15] and by its use we have effected permanent repairs in a number of cases in which there had been relapse after repeated operations by other methods.

REFERENCES

1. Martin: "Medical and Surgical Gynecology," Pozzi, vol. i, p. 499.
2. Stoltz: "Medical and Surgical Gynecology," Pozzi, vol. i, p. 508.
3. Alexander: "Surg., Gyn., and Obst.," vol. vii, p. 408; "Text-book of Gynecology (Wood)," second ed., p. 594.
4. Watkins: "Surg., Gyn., and Obst.," May, 1909, pp. 471–479.
5. Wertheim: "Surg., Gyn., and Obst.," January, 1907, pp. 1–10.
6. Frankenthal: "Jour. Amer. Med. Assoc.," July 3, 1909, pp. 16–22.
7. Mackenrodt: "Monatsschr. f. Geb. u. Gyn.," 1896, vol. iv, p. 489.
8. Kocher: "Text-book of Operative Surgery," 1911, p. 706.
9. Crile: "Cleveland Med. Jour.," July, 1905.
10. Eastman: "Surg., Gyn., and Obst.," 1911, vol. xii, pp. 160, 161.
11. Tait: "Medical and Surgical Gynecology," Pozzi, vol. ii, p. 363.
12. Harris: "Jour. Amer. Med. Assoc.," December 9, 1899, pp. 1450–1457.
13. Hill: "Jour. Amer. Med. Assoc.," April 4, 1908, pp. 1101–1108.
14. Pilcher: "Ann. Surg.," 1906, vol. xliv, pp. 275–280.
15. Noble: "South. Med. Jour.," April, 1909, pp. 607–612.

DUCTLESS GLANDS

THE DIAGNOSIS OF DISEASES ASSOCIATED WITH ENLARGEMENT OF THE SPLEEN *

H. Z. GIFFIN

The following review of the diagnosis of the various forms of splenomegaly is introductory to a report of the clinical findings in a group of cases occurring in our experience in the Mayo Clinic, which will appear later.†

Examination of the liver and spleen at the time of operation has stimulated the interest of the surgeon in diseases which have been hitherto regarded as entirely medical. This interest will result in adding to our knowledge of the relative functions of the organs of the upper abdomen, and will eventually assist in making the classification of hepatic and splenic diseases more nearly definite. That one may be in the receptive mood, it is, therefore, necessary to become as familiar as is possible with the diagnosis of diseases associated with splenomegaly.

The exact degree of enlargement of the spleen is usually not determined until an edge is palpable below the costal margin. That the outline of the spleen by percussion is uncertain because of its situation is not an excuse for the more or less general carelessness exhibited in examining for the size of the spleen as a matter of routine. The spleen may lie high and be enlarged transversely, and in this event a definite splenomegaly may be overlooked. Perisplenitis is a frequent surgical and pathologic finding, and it

---

*Read before the Minn. State Med. Soc., August, 1912. Reprinted from "Journal-Lancet," February 15, 1913, pp. 97–100.

†An article by the author ("Clinical Observations Concerning 27 Cases of Splenectomy") will appear later in the "Amer. Jour. Med. Sci." Articles dealing with the surgical and pathologic conditions will be published by W. J. Mayo and L. B. Wilson in a forthcoming number of "Surg., Gyn., and Obstet." See also W. J. Mayo: "Jour Amer. Med. Assoc.," January 1, 1910, vol. liv, pp. 14–17.

is quite likely that clinical evidence of this condition is not obtained as often as it should be.

If a patient with a palpable enlargement in the region of the spleen presents himself for examination, it is, of course, first essential to determine positively whether or not the organ be spleen, and this distinction is not always easy. The question will usually lie between spleen and kidney. If one can feel edge and notch, there is no difficulty, but it is sometimes impossible to demonstrate the characteristic contour. The edge of the spleen, like the edge of the liver, may at times be revealed by pressing the mass forward and toward the median line, at the same time everting the anterior portion. Similarly, the organ may be pressed into the loin and its edge everted. Often the kidney may be demonstrated as a separate mass lying posteriorly. By these means a difficult diagnosis may be made simple. At times, however, the only certain method of arriving at a conclusion is by means of cystoscopic and pyelographic examination. The development of pyelography assures reasonably accurate information as to the existence of a tumor of the kidney, and pyonephrosis, hypernephroma, and cystic kidney have so resembled the spleen as to make a diagnosis impossible without this procedure, and perfectly definite with it. The position of the kidney, as demonstrated by the injection of colloidal silver, may be compared with the position of the tumor at the time of exposure, taking into consideration the focus used in making the radiogram.

Movable and *wandering spleens* are occasionally seen, and, upon superficial examination, may be diagnosed as movable kidney. The spleen may descend as low as the pelvis. If, however, the occurrence of wandering spleen be kept in mind, the organ can usually be recognized by its contour. Two cases of wandering spleen have been operated on in the Mayo Clinic. Another patient had been operated on elsewhere for movable kidney, apparently as the result of a mistaken diagnosis. The kidney had been stitched up, but the tumor, which, upon palpation, showed all the characteristics of spleen, remained as movable as before.

Upon first consideration it would appear that tumors of the stomach and intestine could not be confused in the diagnosis of splenomegaly. During the last year, however, the writer has seen two cases in which a large carcinomatous mass could not be differentiated from enlargement of the spleen before operation. The absence of a history of gastric symptoms, negative findings upon gastric analysis, the demonstration of an edge, and the location of the tumor led us to regard the tumor as most likely spleen, although the contour was not typical enough to warrant a positive diagnosis. One of these cases had been diagnosed previously as splenic anemia by an internist of great experience.

An intestinal tumor will more often simulate the kidney than the spleen. The left lobe of the liver may be enlarged in such a way that its edge descends at the left costal border and is thus confusing. Omental tumors must be differentiated from movable spleen. If the splenic dulness can be definitely outlined by percussion, a diagnosis may be made by exclusion.

The spleen may be moderately enlarged for years without apparent injury to health. Osler[1] reports having seen a group of such cases in women without anemia and from no evident cause. On several occasions we have observed in Greeks a moderate enlargement of the spleen without complaint or indicative findings. Some of these doubtless had had malaria. Cabot[2] has noted that other peoples from southern Europe present the same condition.

While the slight enlargement of the spleen seems to occur without harm, it must also be remembered that splenic enlargement sometimes precedes the development of anemia by several years in certain cases of splenic anemia, and the spleen must be looked upon as a possible source of future trouble, especially if it be of considerable size. Its removal may then be considered.

The spleen may be temporarily enlarged in many of the *acute infections of childhood,* also in *rickets* and other forms of *malnutrition* in babes. The enlargement of the spleen which occurs with *typhoid fever, generalized tuberculosis,* and *malaria* need only be mentioned. In connection with tuberculosis it must not be forgotten that a marked tuberculous enlargement of the spleen may occur without evidence of tuberculosis elsewhere. In some of the reported spleens, however, the tuberculous process seems to be less prominent than the general hyperplasia. One patient of this type was operated on in the Mayo Clinic in 1904 and made a good recovery, but died four months later. Franke[3] has collected 10 such operative cases. It is not likely that this type of splenomegaly will be differentiated from splenic anemia unless tuberculosis can be demonstrated elsewhere in the body. The spleen of malaria has been removed when other treatment has failed to prevent the return of attacks. The diagnosis is usually made easily; in fact, there is a temptation to ascribe splenic hypertrophy to malaria when it may have no etiologic relationship.

Syphilis of the spleen should always be considered as a possibility in every patient with splenomegaly, and a Wassermann reaction should not be neglected in any questionable case. The frequency of syphilis seems to be quite generally appreciated at the present time, so that this error is less likely to occur today than it was ten years ago. Syphilitic cirrhosis of the liver with splenomegaly is of comparatively frequent occurrence, and the difficulty of obtaining a history of infection is notorious. Congenital syphilis of the spleen is not rare in children. There is, however, a *non-luetic cirrhosis* of the liver which occurs in children; ascites and moderate enlargement of the spleen are present.

Primary sarcoma of the spleen is rare; the growth of the organ is rapid. Twenty-five cases have been reported and are reviewed in a paper by Bush.[4] Eleven of the 25 were diagnosticated at autopsy, while in 14 splenectomy was done, with 4 operative deaths. Two remained well for several years. Pathologists agree that a positive diagnosis of sarcoma of the spleen is often hazardous, and when recurrence does not follow, there is a possibility that the tumor was in reality a benign *lymphoma* (Türk[5]; Sternberg[6]). One patient in whom splenectomy was done at the Mayo Clinic for what was morphologically lymphosarcoma has remained well for seven years. In another case a diagnosis of lymphoma was made and the patient has remained well for a year and one-half.

Clinically these two cases presented the syndrome of splenic anemia.

The *Gaucher type of endothelioma* of the spleen is regarded by some observers as a true tumor. Clinically, however, these cases may not be differentiated from splenic anemia, although Brill[7] has suggested certain points which may be of assistance in diagnosis. Three spleens of this type have been removed in the Mayo Clinic. The clinical histories were those of splenic anemia.

Cystic spleen may be difficult to differentiate from cystic kidney and cyst of the pancreas. Cyst of an aberrant duct of the liver in the left triangular ligament has been reported. Cysts occur in the spleen in about 3 per cent. of patients with hydatid disease. Of non-parasitic cases, 42 instances have been reported (Musser[8]). *Fibroma* of the spleen is rare. *Carcinoma* of the spleen is secondary, and uncommon in occurrence. *Infarcts* in arterial disease and *abscess* in infectious diseases may cause splenic enlargement.

Pernicious anemia may be associated with enlargement of the spleen, and, if the blood-findings be not typical at the time of examination, a diagnosis may have to be deferred. The spleen is usually not large, and in this there is a contrast with splenic anemia and Banti's disease. Occasionally the coexistence of a very large spleen and an atypical blood-count leads to a questionable diagnosis.

Lymphatic and myelogenous leukemia need only be mentioned, as the blood-pictures are pathognomonic. Care, however, must be taken if leukemia be seen in the aleukemic stage. It must not be forgotten that an enlarged spleen accompanies *polycythemia*. The term *pseudoleukemia* is indefinite, and should probably be reserved for that condition in which lymphocytic infiltration of the viscera occurs, without the characteristic blood changes of lymphatic leukemia. There is a low leukocyte count with lymphocytic increase, enlargement of liver and spleen, and slight enlargement of the lymphatic glands. The microscopic examination of an excised gland shows hyperplasia. This condition often occurs in children, and may be, in reality, some one of the other forms of anemia in which the blood-picture has been altered by reason of its attack upon a youthful rather than an adult organism. The diagnosis of the diseases of the blood in children is very uncertain at best. Secondary anemias occurring with rickets and congenital syphilis may give blood-pictures suggestive of pernicious anemia, lymphatic leukemia, myelogenous leukemia, or splenic anemia.[9] Consequently, when an abnormal blood-picture is obtained in an infant, the possibility of nutritional disturbances must, first of all, be considered.

Splenic anemia seems to be a fairly definite *clinical* entity, although many observers prefer to look upon it as a symptom-complex. It is described as a disease of unknown origin, presenting a progressive enlargement of the spleen; a chronic course of from months to ten years and even twenty years; an anemia of the secondary type, generally with leukopenia; a tendency to hemorrhage, especially to hematemesis; a certain degree of pigmentation in the late stages; and a secondary cirrhosis of the liver, with or without ascites. The histories of these cases seem to indicate that the splenic change is primary. Enlargement of the spleen may be present for years before the development of anemia. An absence of leukocytosis seems to be an almost constant finding. Leukocytosis, save after hematemesis, should, therefore, make one suspicious of some condition other than splenic anemia. The spleen of splenic anemia is often very large, and in this it differs from the spleen of hepatic cirrhosis. In *cirrhosis* the liver changes seem to precede the splenic enlargement, while the reverse is true in splenic anemia. In cirrhosis again the anemia is less marked, and an etiologic factor of cirrhosis may be present. *Hanot's cirrhosis,* presenting a moderately enlarged spleen, occurring in young people without a history of the usual causes of cirrhotic liver, and accompanied by a chronic jaundice, should not be difficult of differentiation. In *hemochromatosis* the changes in the liver and the splenic enlargement are concomitant, and the deposition of iron pigment in the skin and viscera and, later, diabetes, as a result of involvement of the pancreas, form a definite clinical picture. Splenic enlargement may also occur in *Hodgkin's* *disease.* In late Hodgkin's disease the splenic and hepatic hypertrophy may be prominent, while the size of the lymphatic glands may decrease and a leukopenia occur, giving a clinical picture which at first sight may suggest splenic anemia.[10] The history of the early involvement of a group of glands, however, usually points the way to a diagnosis. The excision and microscopic examination of a gland will often give positive evidence. In the *family type* of *hemolytic jaundice* with splenomegaly the jaundice may be absent temporarily, and the condition may thus be confused with splenic anemia.[11] *Acute infectious epidemic jaundice* (Weil's disease) would give no difficulty because of its clinically acute infectious nature. As previously noted, syphilis of the spleen must always be kept in mind and carefully excluded.

There is a group of cases simulating the clinical picture of splenic anemia, and, in addition, presenting findings suggestive of an acute or subacute infectious process. The fever may be remittent or intermittent and accompanied by chills. Attacks may last two or three months at a time, and may recur at intervals of several months, or the condition may be an acute one, giving a history of several months' illness. The size of the spleen and liver may be much reduced between attacks, and the patient may return to good general health. Leukopenia is present save at the time of chills and high fever. Blood cultures are negative, and no evidence of syphilis, malaria, or tuberculosis can be detected. Two cases with these characteristics have been observed by the writer. Are these cases acute types of splenic anemia, or is the clinical course the result of phlebitis of the splenic vein or other branches of the portal system, a condition which has been reported in the autopsy findings in certain cases? The condition may be due to a more or less generalized chronic infectious process. In view of the fact that *kala-azar,* with its enormous enlargement of liver and spleen, may make its appearance at any time, it is imperative, in cases of the foregoing type, to examine the peripheral blood, the blood obtained by splenic puncture, or an excised cervical gland, for the presence of Leishman-Donovan bodies.

In all, 27 splenectomies have been done at the Mayo Clinic from April, 1904, to July, 1912. Of these cases, 18 conformed most nearly to the group commonly regarded, from a clinical standpoint, as splenic anemia.

A review of the diseases associated with enlargement of the spleen impresses one with the fact that exhaustive examinations and complete notes are necessary if we may hope to arrive at a definite grouping of these obscure conditions. Pathologic and clinical information must be carefully correlated. Certain rare disorders must be kept freshly in mind. Laboratory findings must be utilized in the differentiation more liberally than is ordinarily necessary. One is repaid, however, by the unusual interest attaching to these diseases, especially to those that simulate the symptom-complex of splenic anemia.

REFERENCES

1. Osler: "Amer. Jour. Med. Sci.," 1902, vol. cxiv, pp. 751–770.
2. Cabot: Quoted by Osler, "Amer. Jour. Med. Sci.," 1902, vol. cxiv, pp. 751–770.
3. Franke: "Deut. med. Woch.," 1906, vol. xxxii, pp. 1656–1659.
4. Bush: "Jour. Amer. Med. Assoc.," vol. liv, 1910, pp. 453–456.
5. Türk: "Wien. klin. Woch.," 1903, vol. xvi, No. 39.
6. Sternberg: Lubarsch Ostertag, 1903, vol. ii.
7. "Amer. Jour. Med. Sci.," 1905, vol. cxxix, pp. 491–504.
8. Musser: "Amer. Jour. Med. Sci.," 1911, vol. cxlii, pp. 501–508.
9. Shaw: "Lancet," 1904, vol. ii, pp. 1560–1562.
10. Weber: "Amer. Jour. Med. Sci.," 1911, vol. cxlii, pp. 508–522.
11. Weber and Dorner: "Lancet," 1910, vol. i, pp. 227–232.

CLINICAL OBSERVATIONS CONCERNING 27 CASES OF SPLENECTOMY*

H. Z. GIFFIN

The association of enlarged spleen with anemia occurs in so many diseases and in such a variety of abdominal conditions that a fuller knowledge will be necessary before one can arrive at a correct classification of splenomegaly. The results of medical, surgical, pathologic, and experimental experience must be reported abundantly before a correct grouping can be even attempted.

That a certain picture conforming to splenic anemia as it is clinically described presents itself there is, of course, no doubt. However, the many factors that are discussed by writers on the etiology of this condition at once make one question the advisability of stamping a given case with a certain stencil. Syphilis, malaria, passive congestion as a result of portal obstruction, thrombosis of the splenic or portal veins, the occurrence of Leishman-Donovan bodies, the action of extraneous toxins, the occurrence of hemolysis, the existence of an undemonstrated infectious agent—these have all been considered as factors in the causation of certain cases. And there must be added to this list, after a consideration of the cases herewith reviewed, what appears to be more than an accidental association of disease of the gall-bladder with cases that can properly be diagnosed clinically as splenic anemia. Moreover, at one extreme there are many histories of short duration, or those without the typical symptomatology and cases with atypical blood-count, while at the other extreme there are instances in which cirrhosis of the liver seems to form a slightly more prominent part of the picture than the changes in the spleen. And apart from the clinical and etiologic aspects, there is confusion on the pathologic side. The examination of spleens removed from patients regarded from the clinical standpoint as cases of typical splenic anemia reveals no constant histologic picture. Connective-tissue increase is the common finding, but endothelial or lymphocytic hyperplasia may predominate to such a degree that the picture may even simulate a true tumor.

---

*Read before the Mississippi Valley Medical Association, Chicago, October 22–24, 1912. Reprinted from "Amer. Jour. Med. Sci.," June, 1913. Copyright, 1913, by Lea and Febiger.

Where, then, shall the line be drawn in determining the degree of variation permissible in the cases we are to regard as splenic anemia? However, without entering further into the general discussion of conditions simulating splenic anemia, it is my purpose to present the clinical findings in those cases in which splenectomy has been done in the Mayo Clinic.

The total number of splenectomies from April 6, 1904, to July 5, 1912, is 27. For convenience, these are divided into three groups: (1) Those which conform closely to the clinical syndrome of splenic anemia, 18 in number; (2) cases presenting clinical features which suggest that the splenomegaly was a part of a more or less wide-spread infection, and secondary, rather than primary; and (3) miscellaneous cases.

GROUP 1.—SPLENIC ANEMIA—18 CASES

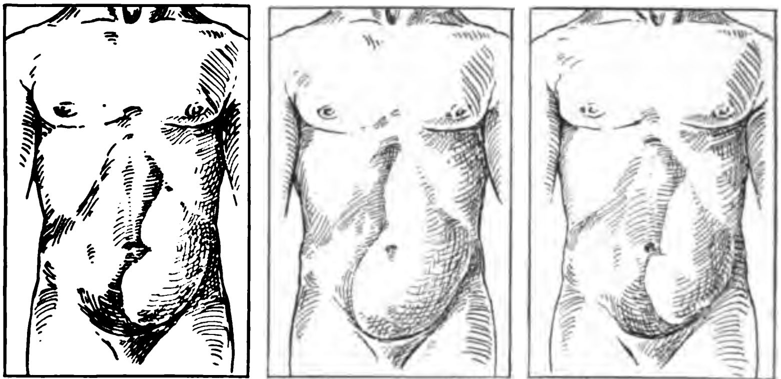
Splenic anemia is at present a *clinical* entity; therefore, in selecting cases for this group the preoperative clinical picture was relied upon. A great and apparently uncomplicated increase in the size of the spleen and an anemia of the secondary type, usually with leukopenia, have been considered essential in the diagnosis. Where the clinical picture was complicated by any condition which would lead one to consider the splenomegaly as a secondary, rather than a primary, process, and likewise when the surgical pathology was definitely that of some other condition, the case was excluded. Two cases in which the spleen showed a predominating lymphocytic hyperplasia, and 3 presenting an endothelial hyperplasia, are grouped as splenic anemia because of their clinical course, and also for the reason that pathologists have not definitely decided that these conditions represent anything more than different types of reaction.

Twelve of the patients were females and 6 males. The youngest patient was twenty-two and the oldest fifty-six years of age. The average age was thirty-seven. The distribution as to decads was as follows: Between twenty and thirty, 6; between thirty and forty, 4; between forty and fifty, 5; and between fifty and sixty, 3.

Enlargement of the spleen was noted in one case twenty years before operation; in another case, fifteen years, and in a third, ten years. In 8 instances splenic enlargement had been noted less than a year preceding operation, and in the remaining 7 from one to seven years. It is quite probable, however, that splenomegaly had in reality been present for a longer time in many of these cases. In 14 of the 18 cases the enlargement of the spleen had definitely preceded the appearance of anemia. In no case did the occurrence of anemia clearly precede splenomegaly.

The recorded measurements of all the spleens of this group show them to be either large or enormous in size. The average length of the spleens in the 18 cases was 24 cm. All of them save one, which lay transversely, reached below the level of the navel, and 7 extended into the left iliac fossa and beyond the median line. The largest spleen weighed 5280 gm., the smallest, 425 gm. The weight was recorded in each instance; the average weight was 1680 gm. In none of them did the long axis extend diagonally across the abdomen, but lay almost entirely to the left of the median line. It is interesting to note that one spleen lay very high, and the enlargement extended transversely into the epigastrium, only one-eighth of the spleen being palpable below the costal margin.

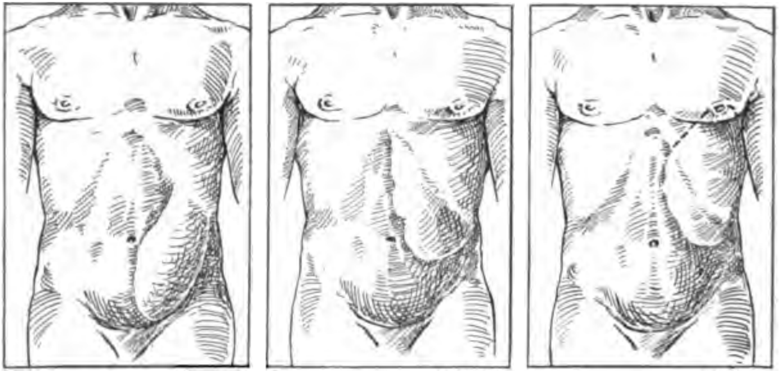
In 4 instances the contour of the spleen was not outlined definitely enough to warrant a diagnosis without the aid of a cystoscopic examination, and in one of these a colloidal silver radiogram was necessary to demonstrate a normal kidney pelvis. Indeed, it may be impossible to diagnose an abdominal tumor positively as spleen without these procedures.



Case 1. P 3539. Splenic Anemia.

Case 2. G 8869. Splenic Anemia.

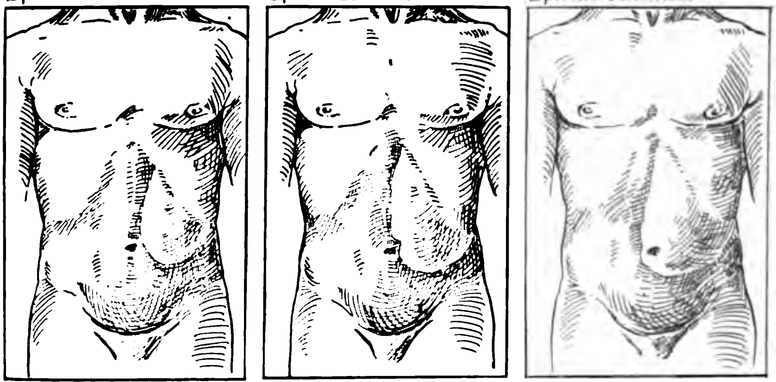
Case 3. P 7074. Splenic Anemia.



Case 4. A 9315. Splenic Anemia.

Case 5. A10324. Splenic Anemia.

Case 6. A18026. Splenic Anemia.

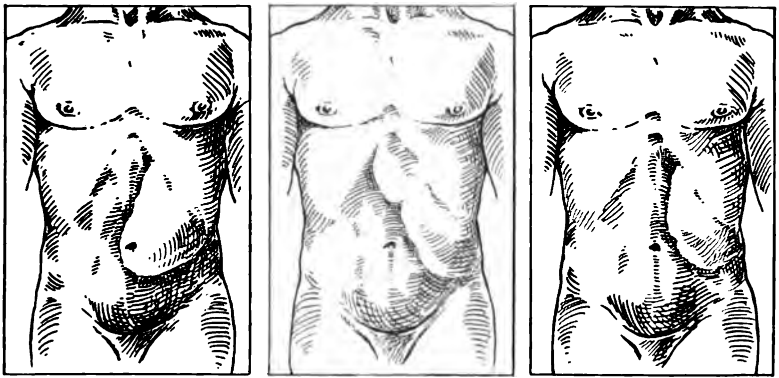


Case 7. A20818. Splenic Anemia.

Case 8. A22026. Splenic Anemia.

Case 9. A27414. Splenic Anemia.

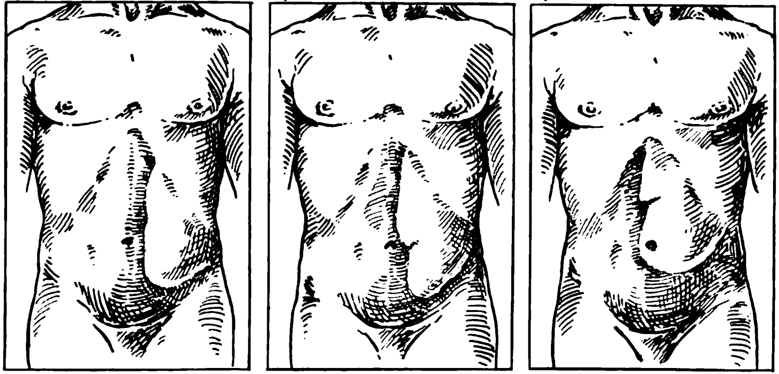
Fig. 160.—Contour and position of spleens as observed clinically before operation.



Case 10. A35431. Splenic Anemia.

Case 11. A39665. Splenic Anemia.

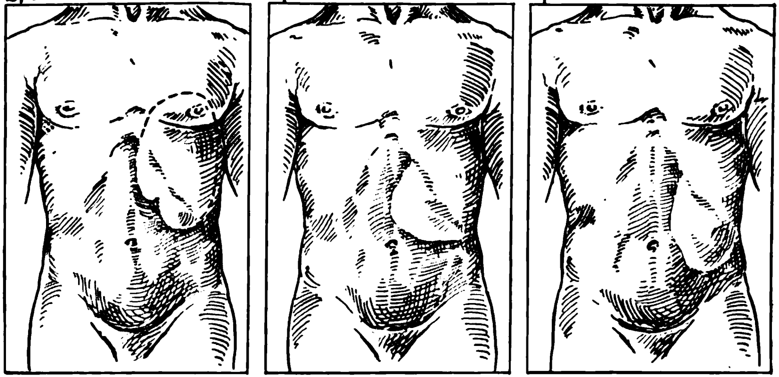
Case 12. A49050. Splenic Anemia.



Case 13. A28194. Splenic Anemia.

Case 14. A58017. Splenic Anemia.

Case 15. A58751. Splenic Anemia.

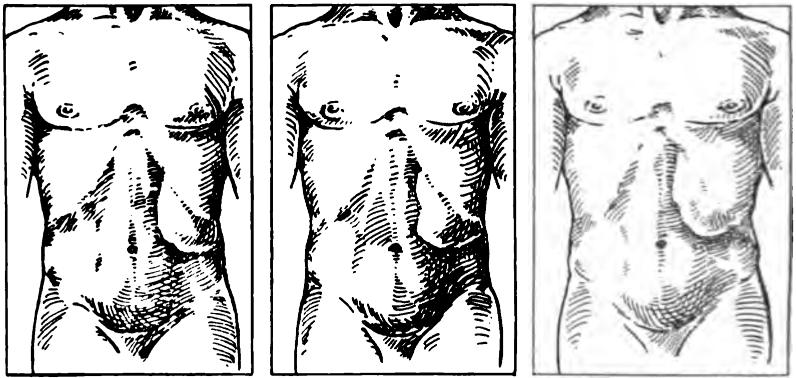


Case 16. A68578. Splenic Anemia.

Case 17. A68788. Splenic Anemia.

Case 18. A69913. Splenic Anemia.

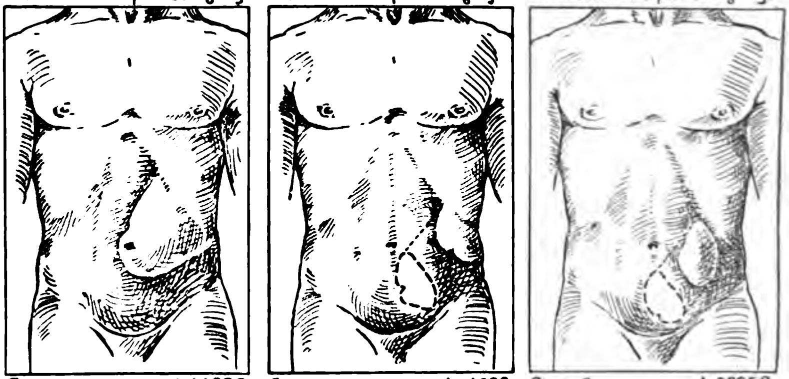
Fig. 161.—Contour and position of spleens as observed clinically before operation.



Case 1. A34196. Infectious ? Splenomegaly.

Case 2. A59392. Infectious ? Splenomegaly.

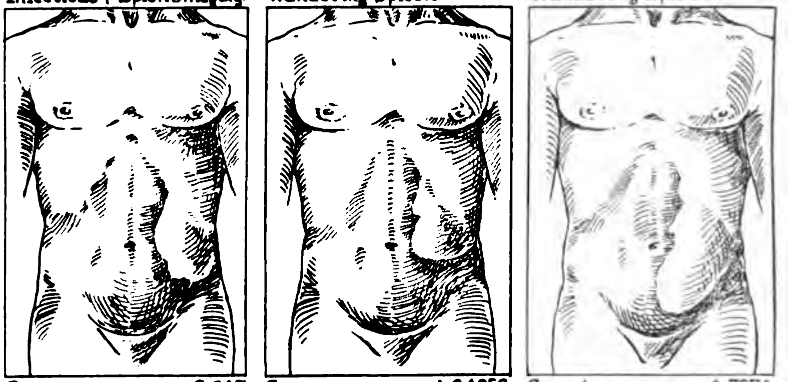
Case 3. A65749. Infectious ? Splenomegaly.



Case 4. A14838. Infectious ? Splenomegaly.

Case 1. A11038. Wandering Spleen.

Case 2. A 82258. Wandering Spleen.



Case 1. G 617. Tuberculosis.

Case 1. A64259. Cirrhosis of Liver.

Case 1. A7074. Atypical Anemia.

Fig. 162.—Contour and positions of spleens as observed clinically before operation.

There was nothing typical about the blood in these cases save that the anemia was of the secondary type, and there was an absence of leukocytosis. The count made within a few days of operation in each case showed a hemoglobin percentage below 75 in all instances save 3; in these there had been a preceding anemia. In most of the cases an attempt had been previously made to improve the condition of the blood before operation was undertaken. In 1 the hemoglobin had been as low as 20 per cent.; in another, 35 per cent. In 10 the hemoglobin had been below 50 per cent.

In 12 instances the leukocyte count was below 5500; in 1, as low as 1000. In only 1 case was a high count obtained (11,000), and this patient had been under the observation of William Osler, who regarded the condition as splenic anemia. The average of the remaining 17 cases was 4200. The occurrence of leukocytosis after operation, as noted by other observers, is corroborated in this series. Pain in the long bones was complained of by several patients after operation.

Differential counts were not distinctly abnormal, save that an occasional normoblast and megaloblast were found. The reader is referred to the accompanying blood-chart for a more detailed conception of the findings.

Hematemesis occurred in 5 of the 18 cases; in 4 of these it was severe. In one case it had occurred every year for fifteen years. Blood in the bowel movement was also present at these times. In one case of Banti's disease in which hematemesis had been severe for nine months the hemoglobin dropped as low as 20 per cent. This patient has been well for three and one-half years following operation. Another patient had had four attacks of bleeding in two years; all were severe. The fourth patient had had two attacks of hematemesis, one of which occurred before splenic enlargement was noted. In the fifth patient the bleeding was merely a regurgitation of blood. There was no instance of bleeding elsewhere than from the gastro-intestinal tract. One additional patient had spat blood probably from the throat at the time of menstruation for three years preceding operation. This has occurred much less frequently since operation.

BLOOD-FINDINGS IN 18 CASES OF SPLENECTOMY FOR SPLENIC ANEMIA

Case No.	Time of Count	Hemoglobin	Erythrocytes	Leukocytes	Small Lymphocytes	Large Lymphocytes	Polymorphonuclears	Myelocytes	Eosinophiles	Basophiles	Transitionals	Normoblasts	Megaloblasts	Poikilocytosis	Polychromatophilia
		Per Cent.			Per Cent.										
1. (P3539)	2 days before operation	50	4,504,000	1,600	..	..	..	..	..	..	..	..	..	..	..
	7 years after operation	70	3,800,000	8,600	..	..	..	..	..	..	..	..	..	..	..
2. (G8869)	2 days before operation	80	5,200,000	4,800	..	..	..	..	..	..	..	..	..	..	..
3. (P7074)	1 day before operation	57	5,080,000	2,000	..	..	..	..	..	..	..	..	..	..	..
	5 years 8 months after operation	85	4,800,000	3,000	..	..	..	..	..	..	..	..	..	..	..
4. (A9315)	2 weeks before operation	40	..	4,600	..	..	..	..	..	..	..	..	..	..	..
	7 months after operation	70	4,280,000	2,700	..	..	..	..	..	..	..	..	..	..	..
5. (A10324)	3 weeks before operation	50	2,960,000	5,600	..	..	..	..	..	..	..	Smears negative			
	1 week before operation	70	..	9,500	..	..	..	..	..	..	..	Smears negative			
	3 weeks after operation	..	..	34,800	4.0	..	93.0	..	3.0	..	..	..	..	..	..
6. (A18026)	3 days before operation	82	..	7,000	22.5	..	70.0	..	3.0	0.5	..	..	..	..	..
7. (A20818)	6 months before operation	20	1,200,000	..	..	..	..	..	..	..	..	..	..	..	..
	2 days before operation	47	3,300,000	2,500	17.5	7.0	73.0	..	1.5	0.5	0.5	..	..	..	..
	10 days after operation	55	..	9,900	5.6	5.0	86.6	..	0.6	..	2.3	..	+	..	..
	3 weeks after operation	45	3,740,000	12,400	6.0	8.0	85.5	..	..	0.5	..	..	..	..	..
	4 months after operation	80	4,000,000	8,700	..	..	..	..	..	..	..	..	..	..	..
	3½ years after operation	90+	5,000,000	8,500	..	..	..	..	..	..	..	..	..	..	..
8. (A22026)	2 weeks before operation	68	3,600,000	2,500	23.0	3.0	72.0	..	..	1.0	1.0	..	..	..	..
	2 weeks after operation	60	4,640,000	7,700	..	..	..	..	..	..	..	..	..	..	..
	4 weeks after operation	68	5,160,000	7,800	19.6	10.4	64.4	..	4.0	0.8	0.8	..	..	..	..
9. (A27414)	3 days before operation	75	4,360,000	11,000	12.3	1.3	80.6	..	3.3	2.0	0.3	..	2	+	+
	1 month after operation	50	3,090,000	28,800	13.0	8.6	72.3	..	3.0	2.3	0.6	..	..	..	..
	3 years after operation	95	5,600,000	10,500	(?)	2.5	79.0	4	7.5	..	..	..	..	+	..
10. (A35431)	2 months before operation	35	3,030,000	3,200	13.6	5.0	78.6	..	1.0	1.0	0.6	1	..	+	..
	1 week before operation	69	4,000,000	3,400	..	..	..	..	..	..	Smears negative			+	..

11. (A39665)	12 days before operation	50	4,550,000	1,000	43.0	19.0	30.0	1	..	2.0	5.0	..	..	+	..
	18 days after operation	75	4,330,000	3,350	35.5	21.0	37.5	..	4.0	1.0	1.0	..	..	+	..
	2 years after operation	90	4,000,000	5,144	..	..	..	..	..	..	..	..	..	..	..
12. (A49050)	6 days before operation	65	5,420,000	3,750	..	..	..	..	..	..	..	..	..	..	..
	2 weeks after operation	67	5,680,000	14,200	16.5	8.5	73.5	..	1.0	..	0.5	..	..	+	..
	2½ years after operation	80	4,960,000	11,750	16.3	6.0	73.3	..	1.0	2.3	1.0	..	..	+	..
13. (A28194)	2 weeks before operation	60	2,950,000	7,900	22.0	2.0	74.0	..	1.0	1.0	..	..	..	..	..
	2 weeks after operation	85	4,800,000	9,200	15.0	4.5	76.0	..	3.0	1.5	..	..	..	+	..
	1 year after operation	90	..	..	..	..	..	..	..	..	..	..	..	..	..
14. (A58017)	5 days before operation	90	4,900,000	3,400	21.5	6.5	68.5	..	0.5	1.0	2.0	..	..	..	..
	3 weeks after operation	89	4,820,000	7,200	26.5	8.0	64.0	..	0.5	..	1.0	..	..	..	..
15. (A58751)	2 weeks before operation	70	3,970,000	4,900	26.7	8.0	60.7	..	4.3	..	0.3	1	..	+	..
	2½ weeks after operation	75	4,760,000	12,500	19.7	6.0	71.0	..	2.7	0.7	..	..	..	..	..
	1 years after operation	100	4,800,000	15,000	Differ	ential	count	not	abno	rmal.	..	..	..	..	..
16. (A68578)	2 days before operation	50	4,200,000	5,100	13.0	2.0	78.0	..	3.3	2.7	1.0	..	..	+	..
	4 weeks after operation	60	4,320,000	15,600	11.0	9.0	77.7	..	1.7	0.3	0.3	1	..	+	..
17. (A68788)	3 days before operation	55	4,600,000	2,700	19.4	8.0	70.0	..	2.0	..	0.6	..	..	++	+
	2 weeks after operation	70	..	14,200	..	..	..	..	..	..	..	..	..	..	..
	5 months after operation	88	4,800,000	10,800	46.7	2.3	45.3	..	1.3	2.0	2.3	..	..	..	..
18. (A69913)	1 week before operation	45	5,080,000	5,500	30.0	9.7	57.0	..	1.7	0.7	0.7	..	..	+	..
	3 months after operation	90	..	..	..	..	..	..	..	..	..	..	..	..	..

NOTE.—A differential count of 200 or 300 cells was made in these cases. All cases save Nos. 4 and 15 gave histories suggesting the intermittent recurrence of anemia. Where many counts were made, a representative selection is given.

The frequent occurrence of pain in the region of the spleen is a noteworthy incident in this series of cases. This symptom has not been generally discussed in connection with splenic anemia, and is probably caused by the perisplenitis which is so commonly present. Infarction may also be a cause of pain. In 12 of the 18 cases there was obtained a history of pain, generally coming in prolonged periods at the left costal arch, and often associated with tenderness. In 6 instances a history of acute attacks of pain was also obtained.

Fever was present in only 2 of these cases while under observation, and was not over 100° F. However, cases regarded clinically as splenic anemia with fever have been reported. Two patients presenting conditions simulating splenic anemia who suffered from high fever, chills, and prostration in periodic attacks have been under our observation. These cases at first consideration seemed to be atypical acute cases of splenic anemia. One of them at exploratory operation showed an advanced cirrhosis of the liver, and an omentopexy was done. The other is included in the second group of this series. Splenectomy was performed, but at operation evidences of gall-bladder disease were found, with many upper abdominal adhesions, and the spleen was not of enormous size. In this patient there were periodic and abrupt elevations of temperature to 105° F., and at the same time the size of the spleen increased and upper abdominal pain of moderate severity was complained of. The condition of the spleen seemed to be secondary to a wide-spread abdominal infection, and not primary.

Diarrhea had been present in only 4 of the 18 cases. One of these was amebic, and occurred in association with malaria ten years preceding operation. In another instance diarrhea had occurred in spells for one year, during which time splenic enlargement had been noted; the stool examination was negative. In the third case diarrhea had been troublesome for nine months, which was about five months preceding splenic enlargement. The fourth patient gave a history of diarrhea which was mild and probably entirely incidental.

A history of malaria was obtained in only 4 cases. In 2 of these there may have existed some direct etiologic relationship. One patient had had malaria nearly every year up to the age of twenty-nine, while splenic enlargement had been noted at times after the age of twenty-three, which was twenty years before operation. Another patient, presenting a typical picture of the ascitic stage of Banti's disease, had had malaria eleven years preceding operation, at which time splenic enlargement had first been noted. It is probable that chronic malaria produces a condition which eventually cannot be differentiated clinically from splenic anemia.

The table of residences is as follows:

Alabama	1
Arkansas	1
Iowa	4
Michigan	1
Minnesota	3
Montana	1
New Mexico	1
New York	1
North Dakota	2
South Dakota	1
Virginia	1
Washington	1

A history of lues was not obtained in any of the cases grouped as splenic anemia. The Wassermann reaction was done on several of the more recent cases and was negative.

Cirrhosis of the liver was diagnosed at operation in 5 of the 18 cases. In 1 additional patient clinical evidence of cirrhosis of the liver developed one year after operation and the patient died later. In 2 other patients the liver was enlarged. In all, then, 8 of the 18 cases showed some change in the liver, while 5 were probably of the Banti type at the time of operation, 2 in the preascitic stage, and 3 in the ascitic stage of Banti's disease. No case showed abdominal fluid without evidence of change in the liver at operation.

Jaundice was noted during the course of the disease twice—once with and once without evidences of cirrhosis. Melanoderma was noted in those cases seen by the writer, but no accurate information as to its occurrence in the series can be given.

CONDENSED TABULATION—18 CASES OF SPLENECTOMY FOR SPLENIC ANEMIA

Case No.	Name	Date of Operation	Sex	Age	Pathology *	Post-operative Condition	Size of Spleen	Weight of Spleen, Grams	Duration of Splenomegaly	Pain—Splenic Region	Size of Liver	Abdominal Fluid	Jaundice	Hematemesis	History of Anemia	History of Malaria	History of Lues	Old Gall-bladder Disease
1. (P3539)	P. G. M.	11-4-'05	F.	41	Lymphocytic hyperplasia	9-24-'12: well	To pelvis	3,275	4 yrs.	Neg.	+(cirrhosis)	+1	Neg.	Neg.	6 mo.	From 8 to 14 yrs.	Neg.	Neg.
2. (G8869)	B. S.	1-7-'07	F.	27	Endothelial hyperplasia	1-7-'07: death day of operation	30 x 20 x 8 cm.	5,280	15 yrs.	2 yrs.	+(cirrhosis)	+3	+1	Neg.	10 yrs.	Neg.	Neg.	Neg.?
3. (P7074)	M.H.M.	5-17-'07	F.	27	Lymphocytic hyperplasia	9-27-'12: well	To pelvis	2,190	1 yr.+	1 yr.	Normal	Neg.	Neg.	Neg.	1 yr.	Neg.	Neg.	Neg.?
4. (A9315)	B. L. T.	5-11-'08	F.	37	Some areas of endothelial hyperplasia	9-25-'12: well	30 x 20 x 7.5 cm.	895	9 mo.+	9 mo.	Normal	Neg.	Neg.	Neg.	?	Neg.	Neg.	Neg.?
5. (A10324)	A. V. L.	7-2-'08	F.	49	Chronic splenitis	Improved for several months: death 5-19-'11	21 cm.	1,450	9 mo.+	Neg.	Normal	Neg.	Neg.	Neg.	9 mo.	Neg.	Neg.	Neg.?
6. (A18026)	H. N.	12-31-'08	M.	26	Chronic splenitis	7-10-'12: well	18 cm.	425	2 yrs.+	2 yrs.	Normal	Neg.	Neg.	Neg.	5 mo.	Neg.	Neg.	Neg.?
7. (A20818)	C. K.	3-4-'09	M.	30	Chronic splenitis	9-25-'12: well	20 cm.	1,180	10 yrs.	4 yrs.	Reduced (cirrhosis)	Neg.?	Neg.	4 times severe	2 yrs.	11 yrs. before	Neg.	Neg.
8. (A22026)	J. D. B.	4-14-'09	F.	53	Chronic splenitis	12-15-'11; death, cause unknown	20 cm.	1,670	3½ mo. (8 yrs.?)	8 yrs.	Normal	Neg.	Neg.	Regurgitation	4 mo.	Neg.	Neg.	Neg.
9. (A27414)	C.M. H.	8-11-'09	M.	45	Chronic splenitis	9-'12, hemoglobin 90 per cent.; cardiac and renal symptoms	32 x 25 cm.	1,514	4 yrs.	4 yrs.	Normal	Neg.	Neg.	Neg.	2 mo.	Neg.	Neg.	Neg.
10. (A35431)	W. J. P.	5-3-'10	M.	39	Chronic splenitis	5-9-'10: death fifth day	25 x 20 cm.	575	15 yrs.?	2 mo.	Normal	Neg.	Neg.	Once a yr. for 15 yrs.	15 yrs.	Neg.	Neg.	+ Stones?
11. (3966 5)	T. O. B.	7-4-'10	F.	50	Chronic splenitis	10-19-'12: well, arthritis deformans	30 cm.	1,385	4 mo.+ (9 mo.?)	3 mo.	Normal	Neg.	Neg.	Neg.	6 mo.	Neg.	Neg.	Neg.
12. (A49050)	F. F.	2-27-'11	M.	23	Chronic splenitis	8-22-'11: well	24 x 20 cm.	879	2 yrs.	Neg.	Normal	Neg.	Neg.	4 times	2 yrs.	Neg.	Neg.	+ Stones
13. (A28194)	R. K.	6-30'11	F.	22	Chronic splenitis	6-29-'12: well	25 x 18 x 8 cm	1,530	7 yrs.	Neg.	+(cirrhosis)	Neg.	+1	Neg.	7 yrs.	Neg.	Neg.	Neg.

14.	(A58017)	E. J. J.	9–7–'11	F.	43	Chronic splenitis	9–23–'12: well	20 x 12 x 8 cm.	610	20 yrs.	5 yrs. +	Normal	Neg.	Neg.	Neg.	5 yrs. +	Up to age of 29.	Neg.	Neg.
15.	(A58751)	C. W.	9–26–'11	F.	25	Some areas of endothelial remains	9–22–'12: well	32 x 20 x 12 cm.	4,500	8 yrs.	6 wk	Normal	Neg.	Neg.	Spat blood with menses	Neg.	Neg.	Neg.	Neg.
16.	(A68578)	A. C.	6–5–'12	F.	56	Chronic splenitis	7–16–'12; improved	18 x 12 x 8 cm.	980	6 mo.+	Neg.	Normal	Neg.	Neg.	Neg.	6 mo.	Neg.	Neg.	Neg.
17.	(A68788)	A. J. S.	6–18–'12	F.	37	Chronic splenitis	11–12–'12: well	20 x 12 x 9 cm.	890	9 mo. 4 yrs.?	Neg.	+2 (cirrhosis)	Neg.	Neg.	Twice	9 mo.	Neg.	Neg.	Neg.
18.	(A69913)	S. H.	7–5–'12	M.	49	Chronic splenitis	8–24–'12: well	19 x 11 x 9 cm.	1,000	2 yrs. (3yrs.?)	2 yrs.	+2 (cirrhosis)	Neg.	+at onset	Neg.	6 mo.	As a boy	Neg.	Neg.

---

* For a discussion of the pathology see "The Pathology of Splenomegaly: A Study of the Operative and Autopsy Material from the Mayo Clinic," by L. B. Wilson, "Surgery, Gynecology and Obstetrics," March, 1913.

The etiologic relationship of gall-bladder disease in connection with splenic enlargement may be of greater importance than is at present believed, both by reason of the possibility of infection and also through some influence upon the circulation in the closely related organs of the upper abdomen. Two cases of this series showed evidence of gall-bladder disease at operation, but the splenic enlargement was so great and the picture of splenic anemia so prominent that these cases have been retained in Group I. Moreover, 3 cases herewith reported in Group II showed gall-bladder disease, giving a total of 5 instances of gall-bladder disease in a group of 27 cases of splenomegaly (18.5 per cent.). This seems to be more than an accidental coincidence. One patient whose case was very interesting in this connection had been operated on when fourteen years of age for gall-stones. The gall-bladder was then removed; there were stones in the ducts and an enlarged spleen was found. Seven years later, when splenectomy was done, a diagnosis of Banti's disease was confirmed at operation. During the interim there had developed a progressive enlargement of the spleen, with recurring attacks of anemia.

During the last two years, while operating for other abdominal conditions, a moderate enlargement of the spleen (3 and 4 times normal) has been noted in 16 cases. In 8 instances it was associated with gall-bladder disease.

The operative mortality in the entire group of 27 cases was 2, or 7.4 per cent. One of these patients was in very poor condition, and death occurred on the day of operation; moreover, this was an early case, the third of the series. In the 18 cases grouped as splenic anemia the postoperative results have been very satisfactory. Of the 16 patients who recovered from operation, 12 are in excellent health for periods varying from six months to seven years, 2 are improved, 1 improved for several months, but later developed ascites and died three years after operation, with symptoms of hepatic cirrhosis, and 1 died two and one-half years after operation—the cause of death unknown. Of the 2 patients reported as improved, 1 shows normal blood, but is suffering from myocardial and renal insufficiency, while the other was operated on six months ago. Four of the 5 patients who showed evidence of cirrhosis of the liver at operation are in excellent health—1 as long as seven years after operation. The results are shown in more detail by the following table:

GROUP I.—POST-OPERATIVE RESULTS

CASES CONFORMING CLINICALLY TO THE SYNDROME OF SPLENIC ANEMIA

CASE NO.	YEAR	TIME AFTER OPERATION	RESULT
1. (P3539)	1905	7 yrs.	Well. Ascitic stage of Banti's disease. Spleen showed lymphocytic hyperplasia.
2. (G8869)	1907	1 day	Operative death. Ascitic stage of Banti's disease. Spleen showed endothelial hyperplasia.
3. (P7074)	1907	5½ yrs.	Well. "Better health than ever." Spleen showed lymphocytic hyperplasia.
4. (A9315)	1908	4½ yrs.	Well. Spleen showed endothelial hyperplasia.
5. (A10324)	1908	3 yrs.	Improvement for several months. Death three years after operation. Ascites and dropsy (hepatic cirrhosis?).
6. (A18026)	1908	4 yrs.	Well.
7. (A20818)	1909	3½ yrs.	General health excellent. Ascitic stage of Banti's disease.
8. (A22026)	1909	2½ yrs.	Death, cause unknown.
9. (A27414)	1909	3½ yrs.	Blood normal. Myocardial and renal insufficiency. No improvement in general health.
10. (A35431)	1910	5 days	Operative death.
11 (A39665)	1910	2½ yrs.	Well. Symptoms probably due to arthritis deformans.
12. (A49050)	1911	1½ yrs.	Well. No hemorrhages.
13. (A28194)	1911	1½ yrs.	Excellent health. Preascitic stage of Banti's disease.
14. (A58017)	1911	1 yr.	Excellent health.
15. (A58751)	1911	1 yr.	Well. Spleen showed endothelial remains.
16. (A68578)	1912	6 mo.	Improved.
17. (A68788)	1912	6 mo.	Gained 25 pounds. Better health than for years. Preascitic stage of Banti's disease.
18. (A69913)	1912	4 mo.	Excellent health.

GROUP II.—INFECTIOUS (?) SPLENOMEGALY—4 CASES

Four cases of this series could not well be classified as splenic anemia. The histories were more or less complicated by the occurrence of other affections, suggesting that splenomegaly was not primary. It will be noted that 3 of the 4 patients eventually died, though there were no operative deaths. The division of these cases, as will be inferred from the histories, was made without any reference to the post-operative course. It is not my purpose to discuss these cases in detail, but rather to give their salient features in order that the evidence for excluding them from Group I may be clear. In many respects this small group of cases is the most interesting of the series.

Case 1 (A34196).—J. E. G., male, aged fifty-five years. The chief complaint in this instance was of recurring attacks of upper abdominal pain of moderate severity. There was no history suggestive of ulcer, and a clinical diagnosis of cholecystitis with splenomegaly was made. The enlargement of the spleen had not been noted before examination. There was nothing in the history which was suggestive of splenic anemia. At operation adhesions were found around the appendix, gall-bladder, and pylorus. The duodenum was bound to the pancreas, and an ulcer may have been present. The spleen weighed only 320 gm., and showed no connective-tissue hyperplasia. Splenectomy was the only operation performed, and the patient is in excellent health one and one-half years afterward.

Case 2 (A59392).—W. P. D., female, aged thirty-seven years. For two years, associated with three successive pregnancies, there were similar attacks of illness, apparently without definite evidence of pelvic inflammatory disease. These attacks were characterized by the recurrence of severe chills and high fever, even to 105° and 106° F., and upper abdominal pain of an indefinite nature. The last attack was the most severe and prolonged. During these attacks the spleen became very much enlarged. Examination and special test were negative for malaria, syphilis, and tuberculosis. Blood-cultures and examination of the blood for Leishman-Donovan bodies were also negative. The patient's general condition was very poor as a result of her protracted illness. Hemoglobin was 70 per cent.; red blood-corpuscles, 4,060,000; white blood-corpuscles, 3100. Differential count was not abnormal. At operation evidence of widespread infection was found. There were adhesions in the pelvis, but particularly about the gall-bladder and common duct was there evidence of old disease. The vessels of the spleen were brittle. The weight of the spleen was 640 gm., and pathologically the organ showed considerable increase in connective tissue. After operation the liver, which had been enlarged, became reduced to normal, and the symptoms abated somewhat. The patient gradually lost weight and strength, however, and died four and one-half months later, with nephritis, which may have been entirely a terminal condition. Anemia never became extreme. An autopsy was not obtained. In this instance the splenomegaly was doubtless part of a peculiar chronic infectious process.

Case 3 (A65749).—J. G., male, aged thirty-three years. This patient presented a rather complex history. What was probably a luetic sore had been present fourteen years before operation: the Wassermann reaction, however, was negative at the time of examination. Nine years and five months before operation hematemesis had occurred. The appearance of blood in the stool had been noted oftener than hematemesis—four times in the last three years. Splenomegaly had been present three years. The blood-count was: Hemoglobin, 92 per cent.; red blood-corpuscles, 5,480,000; white blood-corpuscles, 7600. Differential count not abnormal. The spleen extended to the level of the navel. Pathologically, the spleen showed connective-tissue increase and infarcts. Its size was 21 x 15 x 7 cm., and its weight, 900 gm. Death occurred two months after operation. At autopsy an acute nephritis with cardiac dilatation was found. In addition, tuberculous mediastinal and retroperitoneal lymphatic glands and a duodenal ulcer were discovered. Although the history in some respects suggested splenic anemia, in this case the pathologic findings prevent us from so classifying it. Hematemesis, which occurred before operation, may or may not have been due to bleeding ulcer.

Case 4 (A14838).—B. F. S., female, aged fifty-seven years. Raynaud's disease had been first diagnosed five years before operation in this case, and thyroidectomy for exophthalmic goiter had been performed four years previously. Rheumatoid arthritis had been present for three years. The spleen had been enlarged for three years, with rapid growth for six months, and at the time of operation it extended to the level of the anterosuperior spine of the ilium. The blood-count was: Hemoglobin, 84 per cent.; red blood-corpuscles, 5,600,000; white blood-corpuscles, 21,800. The differential count showed a polymorphonuclear leukocytosis of 93 per cent. At operation the spleen was found to measure 20 x 15 x 10 cm. and weighed 1340 gm. The patient also had gall-stones, which it was thought should be removed later, and the liver was somewhat enlarged. A small piece of pancreas was ligated and cut away with the spleen. The patient died six weeks later, and at autopsy chronic nephritis and chronic general peritonitis were found.

GROUP III

The remaining cases are grouped together for convenience: wandering spleen, tuberculosis, cirrhosis of the liver, and pernicious anemia are considered.

(A) *Two Cases of Wandering Spleen.*—Wandering spleen is, as a rule, readily diagnosed if only the possibility of its occurrence be kept in mind. It has often been mistaken for movable kidney. It has remained unrecognized when simple methods of exclusion and careful palpation would have decided the diagnosis definitely. One of these patients (A11038) was neurotic, but complained of pain over the spleen to a degree which seemed to warrant splenectomy. A moderate grade of anemia was present. Four years after operation the patient's blood-count is normal, though she complains of many neurotic symptoms. The second patient (A62258) had complained of recurring attacks of pain of an hour's duration for a period of four years. At operation a twisted pedicle was found, while the spleen could be moved to the lower abdomen and to the right of the median line, though it lay naturally opposite the navel. This patient is well.

(B) *One Case of Tuberculosis of the Spleen* (G617).—Multiple abscesses and tuberculous deposits studded the organ, giving the appearance so commonly seen in the kidney. The length of the history had been sixteen months, and no definite evidence of tuberculosis was found elsewhere in the body before operation. The patient died four months later, however, with evidences of a disseminated tuberculosis. An autopsy was not obtained.

(C) *One Instance Where Cirrhosis of the Liver Seemed to be Primary* (A64259).—Although the patient was only twenty years of age, all parts of the liver were covered with contracted areas, while in volume the organ was increased. It was the opinion of the surgeon (W. J. Mayo) that the cirrhosis was primary. The weight of the spleen was 750 gm., and there was nothing in the pathology which indicated lues. This patient gave a history of splenomegaly for one year and recurrent anemia for two years. The blood-count showed a secondary type of anemia, with a hemoglobin percentage of 58. The leukocyte count was 4200. The patient developed ascites and died two months after operation. An autopsy was not obtained.

(D) *One Case of Pernicious Anemia* (?) (A7074).—In this instance the hemoglobin was low (45 per cent.); the color-index was high, but less than 1, and a few normoblasts and megaloblasts were found in the smears. After operation, however, a shower of normoblasts and megaloblasts occurred. The spleen extended below the navel, and weighed 1640 gm. The patient, two and one-half years after operation, states that he is weak and anemic and unable to work, and a review of the case suggests the diagnosis of an atypical pernicious anemia. It has been impossible, however, to obtain a recent blood-count, and the diagnosis at best remains very uncertain.

STATISTICAL SUMMARY

Total number of splenectomies		27
Operative deaths		2 (or 7.4 %)
Group I. Splenic anemia		18 cases
Well from 6 months to 7 years (longer than 1 year, 10)		12
Improved (1, blood normal, myocardial and renal insufficiency; 1 operated on 6 months ago)		2
Improvement several months; death 3 years after operation (hepatic cirrhosis?)		1
Death 2½ years after operation, cause unknown		1
Operative deaths		2
Total		18
Banti's syndrome (included above)		5
Operative death		1
Well (7 years, 3½ years, 1½ years, 6 months)		4
Spleens showing chiefly connective-tissue hyperplasia		13
Spleens showing lymphocytic hyperplasia (included above)		2
Spleens showing endothelial hyperplasia (Weichselbaum or Gaucher type)		3
Group II		4 cases
Infectious (?) secondary splenomegaly		4
Well	1	
Died from 2 to 6 months	3	
Group III. Miscellaneous		5 cases
Wandering spleens, well	2	
Tuberculosis, death in 4 months	1	
Atypical anemia (?), unimproved 2½ years	1	
Cirrhosis of liver, death 2 months (ascites)	1	

A consideration of this series of cases in which splenectomy was done impresses one with the fact that a proper grouping of conditions in which marked enlargement of the spleen is associated with an anemia of the secondary type is extremely difficult, if not impossible, at the present time. The clinical features form the best basis for a tentative classification, and especially assist us in recognizing clear-cut and uncomplicated cases of splenic anemia. The pathology of splenic anemia and those conditions which simulate it are too little understood, and conclusions for the present would best be drawn only from those reported cases in which pathologic as well as clinical evidence has been published.

This review may also have indicated a possible relationship between gall-bladder disease and splenomegaly. It seems to have indicated more clearly, however, that there is a clinical syndrome conforming to the general conception of splenic anemia in which splenectomy is followed by a return to excellent health in a large percentage of cases, but in those instances in which the diagnosis is complicated by other diseases of a chronic infectious nature the value of splenectomy is questionable.

It is necessary in these, as it is in other medicosurgical conditions, for the physician to learn the details of surgical prognosis. Splenectomy should be advised only after careful diagnosis, not only of the abdominal enlargement itself, but also of the patient's general condition, and after the elimination of the existence of serious complications.

Note.—The reader is referred to the following articles: "Principles Underlying Surgery of the Spleen, with a report of 10 Splenectomies," by W. J. Mayo, "Jour. Amer. Med. Assoc.," January 1, 1910; "Surgery of the Spleen," by W. J. Mayo, "Surgery, Gyn., and Obst.," March, 1913. "The Pathology of Splenomegaly. A Study of the Operative and Autopsy Material from the Mayo Clinic," by L. B. Wilson, "Surg., Gyn., and Obst.," March, 1913.

SURGERY OF THE SPLEEN*

WILLIAM J. MAYO

We have acquired a fairly exact knowledge of the function of all the organs contained in the abdomen with the exception of the liver and the spleen, two organs which are closely associated in their physiology and pathology.

The liver is essential to life. One of its chief functions is to receive the products of gastro-intestinal absorption and change them into tissue-building material.

The spleen is not essential to life. It performs for the general circulation a function somewhat analogous to the digestive organs, removing from the blood broken-down corpuscles and other material of probable nutritive value, which is sent as part of the portal circulation to the liver for further elaboration. It is also concerned in the metabolism of iron.

In its ontogeny, the spleen possibly goes back to a time before the development of the cerebrospinal nervous system. This is indicated by the fact that its only known nerve-supply consists of filaments derived from the splanchnic sympathetic to the capsule, stimulation of which causes contraction. It is an organ of internal secretion controlled by chemic stimulation through the blood-stream, in many respects resembling the liver. We may surmise that this form of stimulation has been quite adequate for function, otherwise the spleen would be more closely associated with the sympathetic ganglia, as are the adrenals, the hypophysis, and other bodies of internal secretion. The internal secretions of the adrenals and hypophysis produce their effect not only by chemic stimulation through the blood, but also by direct action on the sympathetic ganglia, which enables a very small amount of secretion to produce wide-spread results. Evidently the internal secretion of the spleen is not important, since splenectomy does not produce serious results, the associated organs taking up the function.

---

*Read before the Clinical Congress of Surgeons of North America, November 11, 1912. Reprinted from "Surg., Gyn., and Obst.," March, 1913.

The liver destroys poisons, both chemic and bacterial, and stands as a gigantic defense of the general circulation. Bacteria picked up in the portal circulation are destroyed in the liver, and, according to Adami,[1] pigmented areas in the liver are derived from the pigment of slaughtered bacteria. Processes in the liver which interfere with function are often accompanied by changes in the size and parenchyma of the spleen, such as the hypertrophied spleen which so often accompanies cirrhosis of the liver; while primary splenic enlargements are sometimes accompanied by secondary cirrhosis of the liver, as is seen in the late stages of splenic anemia (Banti's disease). It is probable that cirrhosis of the liver is caused by poisons sifted from the general circulation by the spleen, or by poisons from the digestive tract carried by means of the portal circulation to the liver.

The celiac axis supplies the blood to the stomach, pancreas, liver, and spleen, showing the primitive association of function, just as the superior mesenteric artery outlines the intestinal tract derived from the midgut and the inferior mesenteric artery outlines the greater part of the alimentary canal derived from the hindgut. All of the venous return from the celiac axis, superior mesenteric, and inferior mesenteric vessels unite to form the portal circulation.

During the early months of fetal life the spleen, the liver, and the bone-marrow, as well as the lymphoid and adenoid tissues of the body, are all concerned in the formation of blood. This primitive function of the liver is lost at an early period, but is continued in the spleen to some extent throughout life.

The spleen is found in all red-blooded vertebrates, and is peculiar in that the blood comes in actual contact with the parenchyma of the organ. In the fetus it appears to have the power of producing both red and white corpuscles. After birth the function of producing red blood-corpuscles is probably lost, although the ability to produce white blood-corpuscles is maintained. Not only is the function of producing red blood-corpuscles lost in the spleen at this time, but it assumes the function of a destroyer of the obsolete red blood-corpuscles. The great size of the splenic artery permits all the blood of the body rapidly to pass through the spleen, which quickly strains out the broken-down cellular elements as well as bacteria and other micro-organisms. The spleen does not appear to have the power to destroy the micro-organisms it captures, therefore the organisms are delivered for destruction to the liver through the portal circulation.

In the perversion of this dual function most of the diseases common to the spleen have their origin. A great overproduction of white blood-corpuscles, associated with an enlarged spleen, constitutes leukemia of the splenic type. An excess of function in the destruction of the red blood-corpuscles produces not only hyperplasia of the spleen, but an attending anemia from which splenic anemia takes its name. The enlarged spleen (ague-cake of malaria) must be considered a conservative hyperplasia in its inception, although in the later stages it becomes the habitat of malarial organisms which it appears unable to destroy or to deliver to the liver for destruction.

With the present inefficient methods of diagnosis, a diseased spleen is not often accurately mapped out until its size is made manifest on palpation beyond the free border of the ribs. The deep situation of the spleen, and its relation to the stomach, colon, and intestine, as well as the left thorax, renders accurate outlining before this time open to question; and the fact remains that in the large majority of cases we have no correct knowledge of the actual condition of the spleen until it can be felt at the border of the left hypochondrium.

Splenic Enlargements

Myelogenous Leukemia.—Enlargement of the spleen with an excess of white corpuscles is a characteristic of myelogenous leukemia, and the microscopic examination of the blood shows a definite picture which is essential to a diagnosis.

The blood of the most primitive animals is white; in a higher stage of development red blood-corpuscles are found, but they are developed from the white corpuscles. The earliest blood found in the fetus is white, and at this period of development the liver, spleen, lymphoid and adenoid structures of the body, and the bone-marrow are blood-producing organs. Leukemia appears to be a reversion to the embryonic type of blood, in which all of the original blood-making organs have to do with the overproduction of the white cells, just as carcinoma is due to the unlimited production of embryonic epithelial cells, and sarcoma is due to the unlimited production of embryonic connective-tissue cells.

The leukemic spleen has been removed a number of times, and in practically all the cases in which the diagnosis was established the patient died promptly as the result of the operation. Even if this were not the case, since the leukemic spleen is but a part of the general condition, splenectomy would be unavailing.

Splenic Anemia.—This condition is probably a definite entity. Banti,[2] Osler,[3] and later Armstrong[4] describe it as a progressive disease characterized by an enlarged spleen, by a reduction in the number and value of the red blood-corpuscles and low hemoglobin, and often by a reduction in the number of white blood-corpuscles. Clinically, this disease may be accompanied by hemorrhages, especially from the stomach, by progressive weakness, and often by pigmentation of the skin and chronic jaundice. Banti's disease is simply a late phase of splenic anemia. It is marked by splenic hypertrophy, with cirrhosis of the liver, occasionally jaundice, and often ascites.

The condition of the blood in splenic anemia is interesting. As a rule, the red blood-corpuscles drop under 4,000,000, often to 3,000,000, and the hemoglobin to the vicinity of 40 per cent. The white corpuscles vary from 3500 to normal. The differential count is usually unchanged. After the removal of the spleen the blood-picture becomes more nearly normal, although, as a rule, for some months there are variations at different times. When this particular grade of secondary anemia exists in connection with an enlarged spleen and the cardinal symptoms previously mentioned, a diagnosis of splenic anemia can be established, not upon one sign or symptom, but upon the complete clinical picture; and if the disease be uncomplicated, splenectomy may be expected to cure the patient. We have removed the spleen in 18 cases of splenic anemia with gratifying results.

Perisplenitis may exist to such an extent in association with splenic anemia that the spleen cannot be removed without enormous risk to life. Hepatic cirrhosis with perihepatitis may also be present in these cases, the liver and spleen often being encapsulated to a remarkable degree. Because of such complications, splenectomy was abandoned in one of our cases. It is sometimes difficult to determine whether an enlarged spleen with cirrhosis of the liver is a Banti's disease primarily, or whether the splenic hyperplasia is the result of a primary cirrhosis of the liver.

Following splenectomy, there was pain for a time in the long bones in about 25 per cent. of our cases, and in one or two cases a temporary enlargement of the lymphatics, evidently a compensatory hypertrophy of the bone-marrow and glands, as has been noted by Warthin.[5]

There is a type of enlarged spleen of unknown causation not accompanied by anemia—an essential hyperplasia. I have personally observed two cases in which the enlarged spleen had existed —in one case eight years, in the other six years, with the patients in fair health.

Conservative Splenic Enlargements.—The biologic study of micro-organisms found in the blood is interesting. Bacteria such as tubercle bacilli, Bacillus typhosus, pus-producing organisms, etc., are vegetable parasites and are more resistant to chemic poisons, such as mercury bichlorid, etc., than their animal host; therefore bactericids usually fail to destroy them. Methods of treatment based upon increasing bodily resistance through the development of opsonins give the best results in diseases caused by these vegetable parasites. Animal parasites or protozoa, on the contrary, are destroyed by specific poisons, such as quinin for the plasmodia of malaria, mercury for the spirochetes of syphilis, etc. Both vegetable and animal parasites may cause enlargements of the spleen, and in such cases the infectious organisms will be found in the spleen in large numbers. In a few cases of tuberculosis, when the infection was apparently primary and limited to the spleen, the spleen has been removed, with cure of the patient. One case of primary tuberculosis of the spleen came under our observation at St. Mary's Hospital and was operated on. Franke[6] has collected 29 cases of tuberculosis of the spleen, 10 of which were operated on, with 7 cures.

In chronic malaria with hyperplasia of the spleen Jonnesco[7] and various other surgeons have removed the spleen a number of times in such cases with gratifying results.

Movable and Wandering Spleens

A spleen which has developed a complete mesentery, permitting a wide range of motion, is not uncommon, and may be found in the pelvis or passing to the right side of the abdomen. Since such a spleen is subject to more or less traumatism, it sometimes becomes enlarged and appears capable of setting up a marked degree of anemia. Twisting of the pedicle leads to severe symptoms and is not uncommon in these cases. One patient with a somewhat flaccid abdomen and a movable hypertrophied spleen had learned to control attacks of torsion by proper manœuvers to untwist the spleen. Rotation of the spleen, completely cutting off circulation, has occurred in a number of cases, leading to death or splenectomy. Several operations have been devised for reducing and holding a movable spleen in a normal position, but, generally speaking, splenectomy is the wiser plan, since in this class of cases splenopexy does not always relieve symptoms and splenectomy is exceptionally easy and safe. We have operated on 3 cases of symptom-producing movable spleen, one by fixation—a combination of suture and gauze packing. The spleen remained in place, but the patient suffered more or less pain afterward. In 2 other cases (in one of which the spleen was somewhat atrophied) the organ was removed and complete cures followed.

New-growths

Cysts of the Spleen.—The most common form of non-parasitic tumors of the spleen is the cystic spleen, in the great majority of cases primarily due to hemorrhage within its capsule. I refer those interested in this phase of the subject to an excellent article by Powers.[8]

Sarcoma of the Spleen.—Sarcoma is the type of primary malignant disease of the spleen and is rare. Gaucher[9] described a certain proliferation of the endothelium of the venous sinuses as a neoplasm. The tumor of Gaucher must be considered the same type as that of which Weichselbaum,[10] in 1881, reported 2 cases, calling them primary endotheliomas. Jepson and Albert[11] found 32 such cases, in which splenectomy was made in 10. There were 3 deaths and 4 cures in this series, 1 alive six and one-half and 1 four years after operation. In a critical analysis Fowler[12] reduces the 32 cases to 14, which he believes were true sarcomas and the balance nodular hyperplasias. McConnell[13] throws doubt on this data, believing that the cures occurred in cases of chronic hyperplasia and not in the sarcoma group. Pathologists are divided in their opinion as regards these tumors: some hold that they are sarcomas, and others that they are a type of hyperplasia. Histologically, many of these tumors appear to be neoplasms, but are peculiar in that when they exist primarily in the spleen they are comparatively benign, and if removed early may be cured. One patient with lymphosarcoma of the spleen was operated on in our clinic, November 14, 1905, and is in excellent health today. Three cases of the Weichselbaum and Gaucher type of splenic tumor which have been operated on by us were clinically splenic anemias. Two have remained well since, one dying from the operation.

Splenectomy.—It is unfortunate that our main recourse in surgical diseases of the spleen is destructive. As a rule, the disease is advanced before a diagnosis is made, and usually the entire organ is involved, making splenectomy the only rational procedure.

The blood-supply of the spleen can be reduced by ligation of some of the secondary arteries in the hilum. Whether this would reduce its function sufficiently to be of practical value I do not know, but it might be tried in some cases in which splenectomy could not be performed. In the somewhat analogous condition of hyperthyroidism, ligation of the thyroid vessels has given remarkable results.

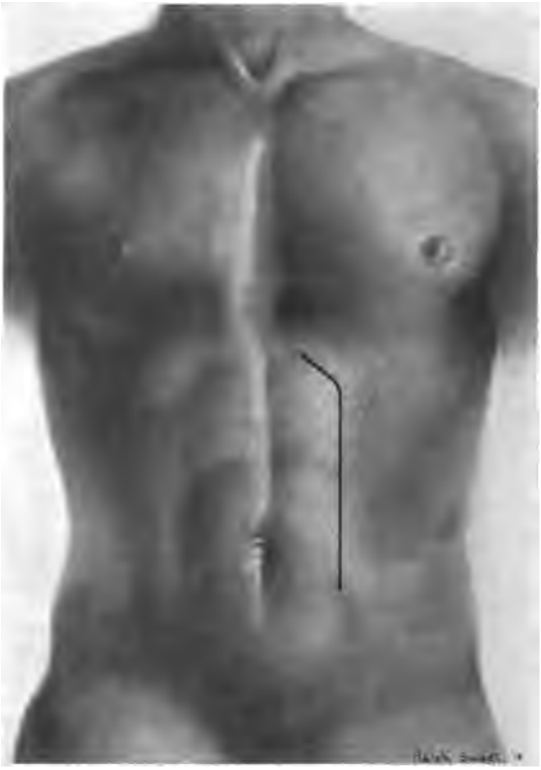


Fig. 163.—Line of incision for removal of spleen.

For the removal of a large spleen an incision is made in the outer margin of the left rectus muscle, extending from the costal arch downward until there is a space sufficient for manipulation. For smaller spleens a transverse incision is practicable. On opening the abdomen the hand is passed over the spleen under the diaphragm, and if adhesions are present, they can usually be broken down with the hand. The spleen can now be brought entirely out

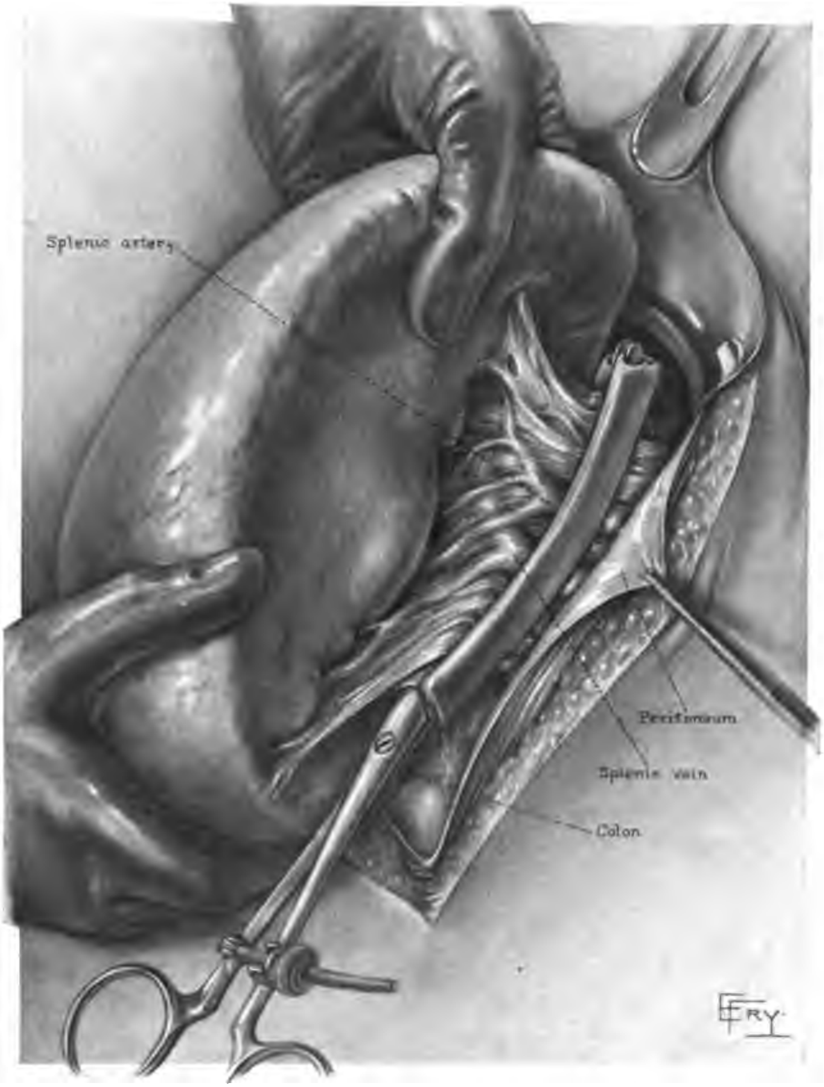


Fig. 164.—Pedicle of spleen controlled by lower forceps.

of the abdominal incision. The fundus of the stomach and the colon come out with the spleen, and these attachments, together with the lienophrenic ligament, etc., can be tied and divided under

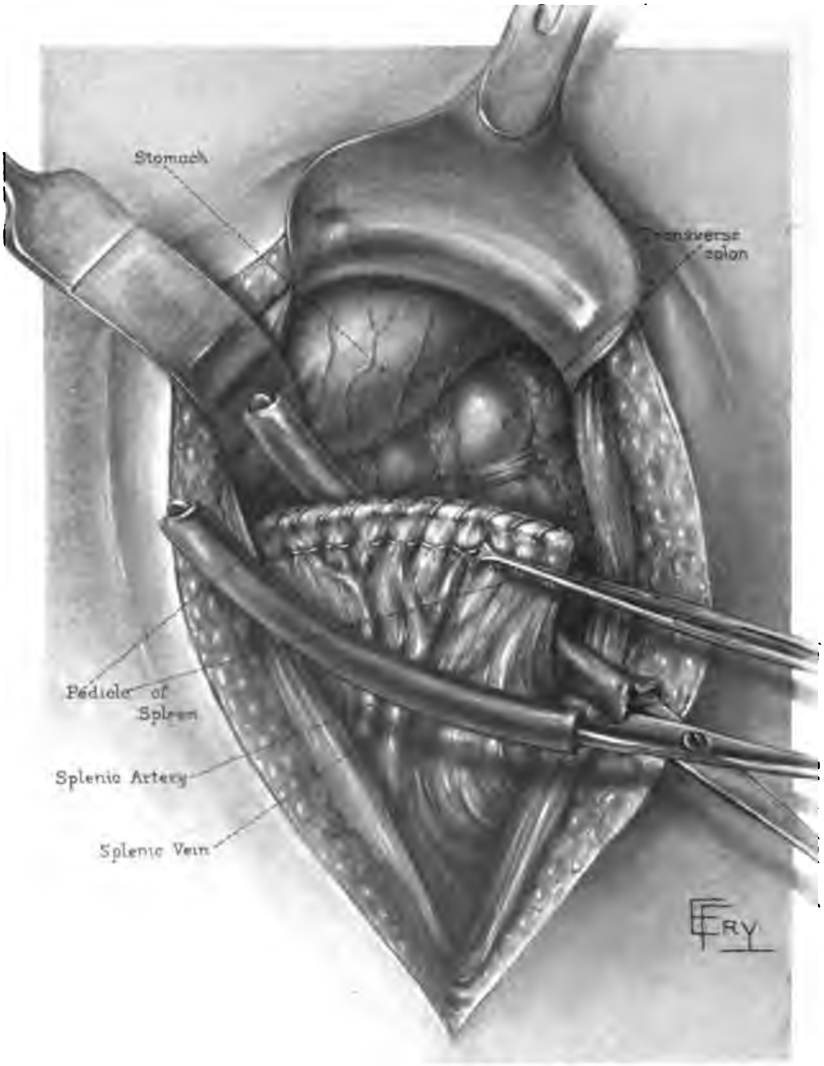


Fig. 165.—Pedicle tied in sections.

inspection. A large gauze pack is carried up into the cavity, from which the spleen has been removed temporarily to check the oozing from the separated adhesions. The spleen is then steadied and all of the attachments tied and divided until it remains attached only by its vascular pedicle. A rubber-covered elastic clamp of the Lower variety is placed on the pedicle, if possible about three inches from the spleen. If portions of the stomach or colon are caught with the pedicle by the elastic holding clamps, no injury will result. This hold prevents slipping and sudden hemorrhage from the great vascular pedicle, and the vessels can be divided close to the spleen into three or four sections and ligated carefully with catgut before the holding clamps are removed.

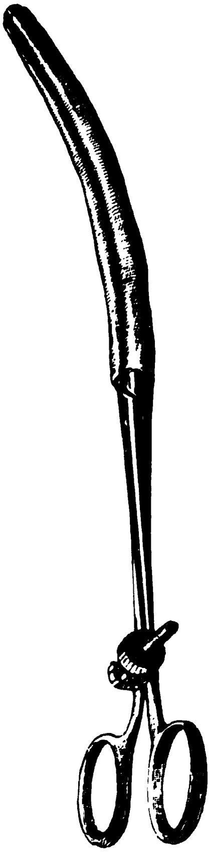


Fig. 166.—Lower's forceps for compression of the pedicle of the spleen.

In hypertrophied spleens of long standing the blood-vessels are often atheromatous, necessitating great care in placing the ligatures. After ligating the vessels, the clamps on the base of the pedicle are loosened gradually, the large gauze pack is removed, and the bleeding points in the deep cavity closed with catgut on a fine needle. In one case I was unable to control the hemorrhage from the under surface of the diaphragm and was compelled to leave a large gauze pack in the cavity, removing it several days later.

The tail of the pancreas is sometimes drawn up with the pedicle and, unless care be exercised, it may be accidentally tied in the pedicle and divided. One and one-half inches of the tail of the pancreas with the pedicle was removed in one of my cases and was not discovered until I was about to drop the pedicle back. After covering the pancreatic stump with peritoneum, I fastened a one-fourth-inch rubber tube with a split in the end to the pancreatic stump with a fine catgut suture and brought it out of a stab wound. This precaution was, however, unnecessary, there being no pancreatic or other drainage, although the pancreatic duct, where it was cut across, was plainly visible.

Accessory spleens, varying in size from a hazel-nut to several inches in diameter, are not infrequently found in the pedicle. If the primary disease be benign, these accessory spleens may be conserved.

The mortality following splenectomy has been estimated to be from 18.5 to 27.5 per cent. Carstens[14] reports 739 cases, with 137 deaths (18.5 per cent.). Johnson[15] found a mortality of 27.4 per cent. in 708 cases. Under present conditions the mortality is much smaller than these statistics appear to indicate. The operation itself, if the patient be in fair condition, should not have a mortality of above 10 per cent. and probably not above 5 per cent. In our 27 cases there were 2 operative deaths.

ANALYSIS OF CASES OF SPLENECTOMY

Mayo Clinic, from April 6, 1904, to October 21, 1912

Total splenectomies	27
Total operative deaths	2

Clinical diagnoses:

Splenic anemia (5 showing Banti's syndrome)	18
Wandering spleen (recovered)	2
Tuberculosis (died in 4 months)	1
Pernicious anemia (?) (unimproved 2½ years)	1
Cirrhosis of liver (death within 6 months, ascites)	1
Infectious (?) splenomegaly	4
Total	27

Operative results in cases of splenic anemia:

Operative deaths		2
Well, 6 months to 7 years		12
Less than 2½ years	6	
2½ years	1	
3½ years	1	
4 years	2	
5½ years	1	
7 years	1	
Total	12	

Analysis of Cases of Splenectomy—(*Continued*)

Improved	2
Death in 3 years; improved until shortly before	1
Death 2½ years after operation; cause unknown	1
Total	18

Pathologic findings in cases of splenic anemia:

Lymphoid hyperplasia (lymphoma (?), 1; lymphosarcoma, 1)	2
Endothelial proliferation (Gaucher type)	3
Chronic diffuse splenitis	13
Total	18

REFERENCES

1. Adami: "Principles of Pathology," vol. ii.
2. Banti: "Ziegler's Beiträge," vol. xxiv.
3. Osler: "Amer. Jour. Med. Sci.," 1902, vol. cxxiv, pp. 751-770.
4. Armstrong: "Brit. Med. Jour.," 1906, vol. ii, pp. 1273-1277.
5. Warthin: "Jour. Med. Research," 1902, vol. vii, pp. 435-463.
6. Franke: "Deut. med. Woch.," 1906, vol. xxxii, pp. 1656-1659.
7. Jonnesco: "Bull. et mém. Soc. de chir. de Bucharest," 1901-02, vol. iv, No. 2, p. 64.
8. Powers: "Trans. Amer. Surg. Assoc.," 1905.
9. Gaucher: "Bull. et mém. Soc. méd. de Hôp. de Par.," 1892, vol. lx, p. 630.
10. Weichselbaum: "Virchow's Archiv," 1881, vol. lxxxv, p. 562.
11. Jepson and Albert: "Ann. Surg.," Philadelphia, 1904, vol. xl, pp. 80-97.
12. Fowler: "Long Island Med. Jour., July, 1911.
13. McConnell; "Boston Med. and Surg. Jour.," February 22, 1912.
14. Carstens: "New York Med. Jour.," November 18, 1905.
15 Johnson: "Ann. Surg.," Philadelphia, vol. xlviii, 1908, pp. 50-65.

THE PATHOLOGY OF SPLENOMEGALY: A STUDY OF THE OPERATIVE AND AUTOPSY MATERIAL FROM THE MAYO CLINIC*

LOUIS B. WILSON

MATERIAL STUDIED

The material for this study consists of the following:

1. Eighteen spleens removed at operation† from patients on whom a positive clinical diagnosis of splenic anemia was made.
2. Six spleens removed at operation† from patients on whom a doubtful diagnosis of splenic anemia was made.
3. Two spleens removed at autopsy from patients on whom doubtful diagnoses of splenic anemia had been made.
4. Two spleens removed at operation† from patients on whom a positive clinical diagnosis of floating spleen was made.

Brief abstracts of the pathologic protocols are herewith presented.

ABSTRACTS OF PATHOLOGIC PROTOCOLS

CASE 1 (P7074).—Female, aged twenty-seven years. Clinical diagnosis, splenic anemia. Splenectomy May 17, 1907. Spleen weight, 2190 grams; exterior smooth; tissue highly vascular; lymphoid tissue very greatly increased; no proliferation of endothelium or connective tissue.

---

* Read before the Minnesota Pathologic Society, November 19, 1912. Reprinted from "Surg., Gyn., and Obst.," March, 1913.

† The clinical aspects of these 26 cases operated on, and also of one case operated on in 1904, from whom no pathologic material is available, will be presented by H. Z. Giffin in an early number of the "American Journal of the Medical Sciences," while W. J. Mayo presents the surgical aspects of the same 27 cases in the March number of "Surgery, Gynecology, and Obstetrics."

Case 2 (P3539).—Female, aged forty-one years. Clinical diagnosis, splenic anemia. Splenectomy November 14, 1905. Spleen weight, 3275 grams; smooth, dark red, very soft; cut surface mottled; enormous increase of lymphoid tissue, which infiltrates connective-tissue bands and vessel-walls; some swelling and increase of endothelium; connective tissue only locally increased. Pathologic diagnosis, lymphosarcoma.

Case 3 (G8869).—Female, aged twenty-seven years. Clinical diagnosis, splenic anemia. Splenectomy January 7, 1907. Spleen weight, 5280 grams; some perisplenitis; exterior of organ smooth; lymphoid tissue much reduced, remaining islets containing numerous large pigmented cells; most of organ made up of large endothelial cells arranged in groups, surrounded by thin walls of connective tissue resembling venous sinuses. (Typical "Gaucher" spleen, with only slight increase of connective tissue.)

Case 4 (A9315).—Female, aged thirty-seven years. Clinical diagnosis, splenic anemia. Splenectomy May 11, 1908. Spleen weight, 895 grams; exterior rough, hard, mottled; gross section shows marked fibrosis; only a few isolated areas of lymphoid tissue (Malpighian corpuscles); bulk of tissue made up of groups of large endothelial cells surrounded by heavy (contracting) bands of fibrous tissue; numerous giant-cells in endothelial groups; accessory spleen shows same histology; primary pathologic diagnosis of tuberculosis; corrected by negative results of examination of alcohol-fixed material stained for tubercle bacilli and of three guinea-pigs inoculated with fresh spleen at time of operation. Patient well when last heard from, two and one-half years after operation. (Typical "Gaucher" spleen with great increase of connective tissue.)

Case 5 (A58571).—Female, aged twenty-five years. Clinical diagnosis, splenic anemia. Splenectomy September 26, 1911. Spleen weight, 4500 grams; exterior surface very rough, nodular, and hard; cut surface mottled throughout with large and small areas of colloid material; lymphoid tissue has almost disappeared; here and there are groups of large endothelial cells, a few well preserved, but most in various stages of degeneration; connective tissue in broad, heavy bands surrounding round, oval, or irregular masses of homogeneous colloid material which seems to have been formed by degeneration of large masses of endothelial cells. ("Gaucher" spleen with colloid degeneration.) Patient well one year after operation.

Case 6 (A10324).—Female, aged forty-nine years. Clinical diagnosis, splenic anemia. Splenectomy July 2, 1908. Spleen weight, 1450 grams; exterior slightly roughened; section tough, hard, with marked fibrosis; lymphoid tissue increased; some swelling of endothelium of sinuses; marked increase of connective tissue. Pathologic diagnosis, chronic diffuse hyperplasia (chronic splenitis).

Case 7 (A18026).—Male, aged twenty-six years. Clinical diagnosis, splenic anemia. Splenectomy December 31, 1908. Spleen weight, 425 grams; exterior rough and hard; cut surface hard, fibrous; lymphoid tissue increased; endothelium of venous sinuses swollen; marked connective-tissue increase. Pathologic diagnosis, chronic diffuse hyperplasia (chronic splenitis).

Case 8 (A20818).—Male, aged thirty years. Clinical diagnosis, splenic anemia (Banti's disease). Splenectomy March 4, 1909. Spleen weight, 1180 grams; exterior slightly roughened and very hard; cut surface firm, with marked fibrosis; lymphoid tissue not increased, but confined to isolated areas (Malpighian corpuscles); endothelium swollen and proliferating in venous sinuses and capillaries which are dilated; connective tissue greatly increased. Pathologic diagnosis, chronic diffuse hyperplasia (chronic splenitis).

Case 9 (A22026).—Female, aged fifty-three years. Clinical diagnosis, splenic anemia. Splenectomy April 14, 1909. Spleen weight, 1670 grams; exterior rough, hard; cut surface mottled ("sago spleen"), firm, and fibrous; lymphoid tissue increased and showing amyloid degeneration in follicles; no material change in endothelium; marked increase of connective tissue. Pathologic diagnosis, chronic diffuse hyperplasia with amyloid degeneration (chronic splenitis).

Case 10 (A27414).—Male, aged forty-five years. Clinical diagnosis, splenic anemia. Splenectomy August 11, 1909. Spleen weight, 1514 grams; exterior surface smooth and organ rather soft; cut surface smooth, slightly fibrous, dark colored; lymphoid tissue greatly increased; endothelium swollen; a few giant-cells; marked connective-tissue overgrowth. Pathologic diagnosis, chronic diffuse hyperplasia (chronic splenitis).

Case 11 (A35431).—Male, aged thirty-nine years. Clinical diagnosis, splenic anemia. Splenectomy May 3, 1910. Spleen weight, 575 grams; exterior rough, mottled, hard; cut surface firm, fibrous, mottled; lymphoid tissue increased, and showing some amyloid degeneration in follicles; endothelium swollen in dilated capillaries and venous sinuses; marked fibrosis. Pathologic diagnosis, chronic diffuse hyperplasia with amyloid degeneration (chronic splenitis).

CASE 12 (A39665).—Female, aged fifty years. Clinical diagnosis, splenic anemia. Splenectomy July 11, 1910. Spleen weight, 1385 grams; exterior surface smooth and soft; section smooth, mottled, soft, dark colored; lymphoid tissue greatly increased; considerable endothelial proliferation in venous sinuses and dilated capillaries; connective tissue increased. Pathologic diagnosis, chronic diffuse splenitis.

CASE 13 (A49050).—Male, aged twenty-three years. Clinical diagnosis, splenic anemia. Splenectomy February 27, 1911. Spleen weight, 879 grams; exterior rough, hard; cut surface firm, hard, fibrous; lymphoid tissue remaining in Malpighian corpuscles only; endothelium of venous sinuses but slightly affected; marked overgrowth of fibrous connective tissue. Pathologic diagnosis, chronic diffuse splenitis.

CASE 14 (A28194).—Female, aged twenty-two years. Clinical diagnosis, splenic anemia (Banti's disease). Splenectomy June 30, 1911. Spleen weight, 1530 grams; exterior smooth, hard; cut surface smooth, firm, dark colored; lymphoid hyperplasia with some small areas of amyloid degeneration in follicles; some proliferation of endothelium in venous sinuses and dilated capillaries; a few giant-cells; marked connective-tissue overgrowth. Pathologic diagnosis, chronic diffuse splenitis.

CASE 15 (A 58017).—Female, aged forty-three years. Clinical diagnosis, splenic anemia. Splenectomy September 7, 1911. Spleen weight, 610 grams; exterior shows marked perisplenitis; cut surface smooth, hard, firm, with marked fibrosis; lymphoid tissue increased; some swelling of endothelium; marked connective-tissue overgrowth. Pathologic diagnosis, chronic diffuse splenitis.

CASE 16 (A68578).—Female, aged fifty-six years. Clinical diagnosis, splenic anemia. Splenectomy June 5, 1912. Spleen weight, 980 grams; exterior smooth; cut surface soft, smooth, dark colored; lymphoid tissue markedly increased; some swelling of endothelium in venous sinuses; a few giant-cells; considerable connective-tissue increase. Pathologic diagnosis, chronic diffuse splenitis.

Case 17 (A68788).—Female, aged thirty-seven years. Clinical diagnosis, splenic anemia (Banti's disease). Splenectomy June 18, 1912. Spleen weight, 890 grams; exterior rough, hard; cut surface mottled, hard, fibrous; marked hyperplasia of lymphoid tissue; considerable swelling and proliferation of endothelium in dilated venous sinuses and capillaries; marked connective-tissue overgrowth. Pathologic diagnosis, chronic diffuse splenitis.

Case 18 (A69913).—Male, aged forty-nine years. Clinical diagnosis, splenic anemia. Splenectomy July 5, 1912. Spleen weight, 1000 grams; exterior smooth, soft; cut surface smooth, soft, dark colored; lymphoid tissue markedly hyperplastic; some swelling of endothelium of venous sinuses and capillaries which are dilated; marked connective-tissue overgrowth. Pathologic diagnosis, chronic diffuse splenitis.

Case 19 (A34196).—Male, aged fifty-five years. Clinical diagnosis, splenic anemia. Splenectomy February 24, 1910. Spleen weight, 320 grams; exterior smooth, soft; cut surface soft, dark; lymphoid tissue much increased; many polymorphonuclear cells; no endothelial proliferation; no connective-tissue increase. Pathologic diagnosis, secondary splenic infection.

Case 20 (A59392).—Female, aged thirty-seven years. Clinical diagnosis, wide-spread upper abdominal infection, acute splenic anemia. Splenectomy October 30, 1911. Spleen weight, 640 grams; exterior nodular; cut surface smooth, with many heavy fibrous bands; lymphoid tissue increased; many areas contain much blood-pigment; no apparent proliferation of endothelium; larger bands of connective tissue thickened, but condition not general. Pathologic diagnosis?

Case 21 (A65749).—Male, aged thirty-three years. Clinical diagnosis, duodenal ulcer. Splenectomy April 3, 1912. Spleen weight, 900 grams; exterior rough, nodular, hard; cut surface shows dilated vessels and marked fibrosis; some increase of lymphoid tissue; venous sinuses contracted; no increase of endothelium; marked overgrowth of connective tissue. Pathologic diagnosis, chronic splenitis.

Case 22 (A14838).—Female, aged fifty-seven years. Clinical diagnosis, Raynaud's disease, gall-stones. Splenectomy June 12, 1912. Spleen weight, 1340 grams; exterior rough, hard; cut surface hard, fibrous; lymphoid tissue reduced; no proliferation of endothelium; venous sinuses shrunken; marked overgrowth of connective tissue. Pathologic diagnosis, chronic splenitis.

Case 23 (A29901).—Male, aged twenty-five years. Clinical diagnosis, splenic anemia. Not operated on; autopsy March 26, 1910. Spleen weight, 1160 grams; exterior smooth, mottled, firm; cut surface hard, fibrous; lymphoid tissue increased; some swelling of endothelium in dilated venous sinuses; marked fibrosis. Pathologic diagnosis, chronic diffuse splenitis.

Case 24 (A7040).—Male, aged forty-five years. Clinical diagnosis, atypical pernicious anemia. Splenectomy February 9, 1910. Spleen weight, 1640 grams; exterior smooth, rather soft; cut surface soft, dark colored; lymphoid tissue increased; no apparent proliferation of endothelium; slight increase of connective tissue; very large amount of débris of broken-down blood-cells and blood-pigment. Pathologic diagnosis, pernicious anemia.

Case 25 (H17130).—Male, aged ten years. Clinical diagnosis, splenic anemia. Not operated on; autopsy December 14, 1905. Spleen weight, 600 grams; exterior pale, hard, fibrous, capsule thickened; cut surface hard, fibrous; lymphoid tissue almost entirely absent; some proliferation of endothelium; advanced fibrosis. Pathologic diagnosis, diffuse chronic splenitis.

Case 26 (A64259).—Female, aged twenty years. Clinical diagnosis, splenic anemia. Splenectomy February 26, 1912. Surgeon's diagnosis at operation, primary hepatic cirrhosis. Spleen weight, 750 grams. Pathologic diagnosis, chronic splenitis.

Case 27 (A62258).—Female, aged twenty-nine years. Clinical diagnosis, painful wandering spleen. Splenectomy January 22, 1912. Spleen weight, 170 grams; organ, both grossly and microscopically, apparently quite normal.

Case 28 (A11038).—Female, aged thirty-nine years. Clinical diagnosis, painful floating spleen. Splenectomy June 27, 1908. Spleen weight, 145 grams; exterior rough, hard; cut surface slightly fibrous, pale; apparently slight atrophy of lymphoid tissue; no change in endothelium or fibrous connective tissue. Pathologic diagnosis, atrophy.

General Discussion

Group I.—Cases with a Positive Clinical Diagnosis of Splenic Anemia.—Of the 18 cases on whom a positive clinical diagnosis of primary splenic anemia was made, all presented the important diagnostic symptoms as laid down by Osler,[33] namely, an enlarged spleen with the following blood-picture: a reduced number of red cells, a reduced number of white cells without material variation from normal in the relative percentages of the several types, no leukocytosis, usually a leukopenia, a very low hemoglobin, and a low color index. In all 18 cases the clinical picture was sufficiently definite to warrant, even after the most critical review, a diagnosis of a secondary anemia apparently due to a primary splenomegaly. Of the 18 cases operated on, 2 died at operation, and of the remaining 16, 11 have remained well for periods varying from six months to seven years. Of the remaining 6, 2 are improved, one died three years after operation with symptoms of cirrhosis, and 2 have not been heard from.

While these 18 cases presented clinical symptoms of such uniformity as to compel the clinician to group them together, the variation in their morbid anatomy is so great that for purposes of pathologic description it becomes necessary to divide them into classes as follows:

Class A.—Chronic Lymphocytic Hyperplasia.—This class contains two cases, Nos. 1 and 2. In the first case, the spleen weighed 2190 grams, and in the second it weighed 3275 grams, or 13 and 19 times the normal weight, respectively (females). In both, the surface was smooth and the tissue was soft and dark red in color. On gross section, both were highly vascular, while the bands of connective tissue, so prominent in spleens in Class III, were notable for their absence.

Microscopic examination of the spleens from these two cases shows in both an enormous increase of the lymphocytes of the parenchyma, with a relative thinning of the stroma and with no material proliferation of the endothelium of the venous sinuses. The lymphoid elements have so increased and so pressed upon adjoining structures as to obliterate all evidence of the Malpighian corpuscles, and, to a great extent, of the venous sinuses (Fig. 167). Besides the increase in the numbers of the lymphocytes, we find a large proportion of them swollen beyond their normal size. This condition of lymphocytic hyperplasia is so marked as strongly to suggest a neoplastic condition. In Case 2 several sections show blood-vessels (Fig. 168) whose walls in limited areas have been so

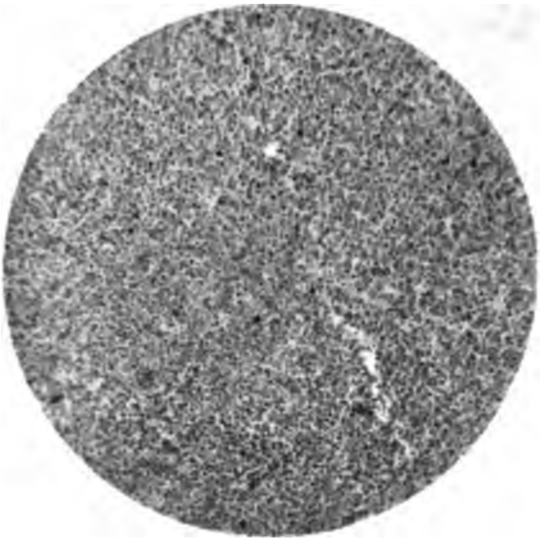


Fig. 167.—Case No. 2. Splenic anemia. Lymphoma type (splenic section × 100, lymphoma area).

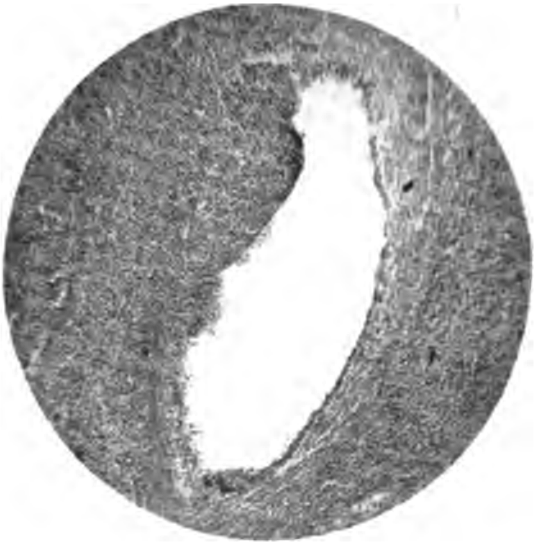


Fig. 168.—Case No. 2. Splenic anemia. Lymphoma type (splenic section × 100, vessel invaded).

infiltrated with lymphocytes that almost no fibrous tissue can be discerned within them.* Sections from areas near the hilum of the spleen from this case also show extensive infiltration of connective-tissue bands by lymphocytes (Fig. 169). These two pictures were so marked that at operation a diagnosis of lymphosarcoma was made from the microscopic slides. A recent careful review of the slides made at the time of operation, and also of freshly made slides, confirms this diagnosis from the histologic standpoint. In the face of this picture, however, the fact remains that these patients, Nos. 1 and 2, who were operated on respectively five and one-half and seven years ago, are both alive and well. It is thus highly improbable that any neoplastic growth existed outside the spleen in either case at the time of operation. When one considers the extent and character of the process in the spleen, it is difficult

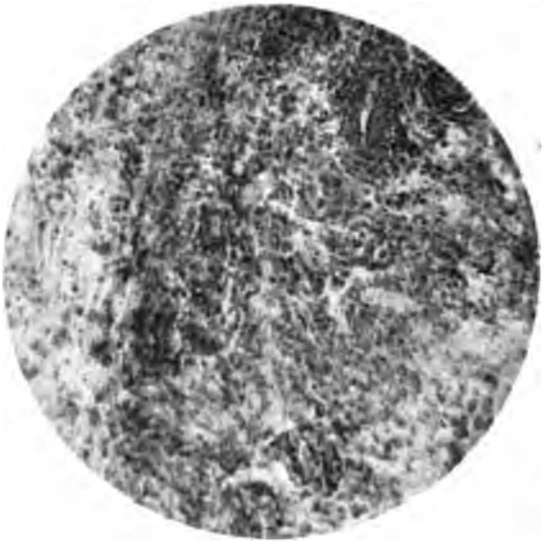


Fig. 169.—Case No. 2. Splenic anemia. Lymphoma type (splenic section × 100, lymphosarcoma).

---

* A similar infiltration by lymphocytes of the arterial walls in the spleen of the normal bat has been noted by Downey and Weidenreich (37).

to conceive how a true lymphosarcoma, as we ordinarily define such, could have so long existed in so vascular an organ without the formation of metastases elsewhere. On the whole, then, it appears that we must materially modify our present concept of what constitutes a lymphoid hyperplasia, or, on the other hand, of what constitutes a lymphoma or lymphosarcoma, before we can place spleens of this type in either class. I am inclined to believe that while, in their final histologic aspects, they may become true neoplasms (lymphosarcomas), both developmentally and clinically, their early stages represent only an extensive lymphocytic hyperplasia, with only a slight return of the cells to their primitive mesoblastic type. They certainly must be considered as quite distinct from such primary sarcomas of the spleen as that reported by Jepson and Albert.[18]

Class B.—Primary Proliferation of the Endothelium of the Spleen ("Gaucher Type").—Our series contains three cases (Nos. 3, 4, and 5), in each of which the spleen presents a picture the most striking characteristic of which is an enormous proliferation of the endothelium of the venous sinuses. Two of these are the largest spleens of our series, No. 3 weighing 5280 grams, 31 times normal (female), and the other, No. 5, weighing 4500 grams, 26 times normal (female). The third, No. 4, weighed but 895 grams, 5 times normal. All these spleens presented a rough exterior. The appearance of the sections, however, both gross (Fig. 170) and microscopic, of the 3 cases varies much.

Case No. 3, which is a typical early "Gaucher spleen," will be described later in detail by Franz Wildner, of this laboratory, who had made considerable study of the case before the final compilation of the data in this paper was begun.

In Case 4 (Fig. 171) the relative smallness of the spleen as compared with the other two cases of the class is readily understood on examination of the microscopic sections. There are only a few isolated areas of lymphoid tissue (Malpighian bodies). Almost all the venous sinuses are crowded with endothelial cells, closely resembling the pictures presented in slides from Case 3 (Fig. 169). In many of the sinuses some or all of the cells are shrunken and have lost their definite outlines, merging into one another and thus showing that they are not only much pressed upon by the connective tissue, but also that they are in an early stage of degeneration.

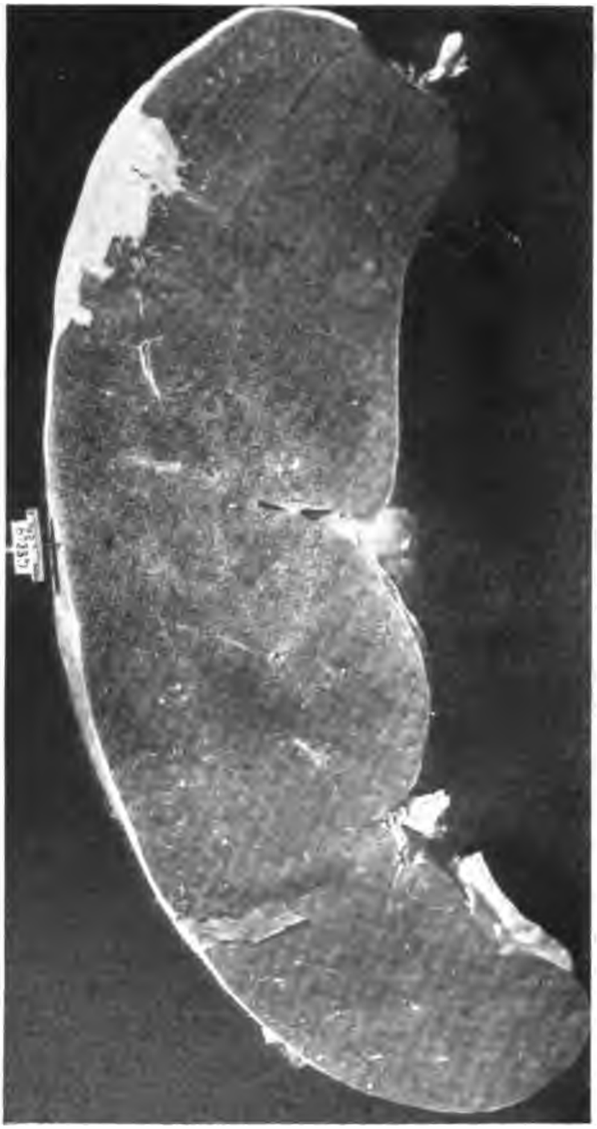


Fig. 170.—Case No. 3. Splenic anemia—Gaucher type (splenic section mottled, marked fibrosis, infarcted).

At the same time, surrounding the sinuses are broad bands of fibrous connective tissue, which give the appearance of having contracted and shut off the circulation from the endothelium of the sinuses. The giant-cells in the venous sinuses in this case are so numerous as to have suggested the possibility of tuberculosis, which, however, has been excluded histologically and biologically. The process has apparently been an initial proliferation of the endothelium with a secondary connective-tissue overgrowth, causing degeneration of the endothelium and a spleen which, while still enlarged (5 times normal), is yet not nearly so large as that in

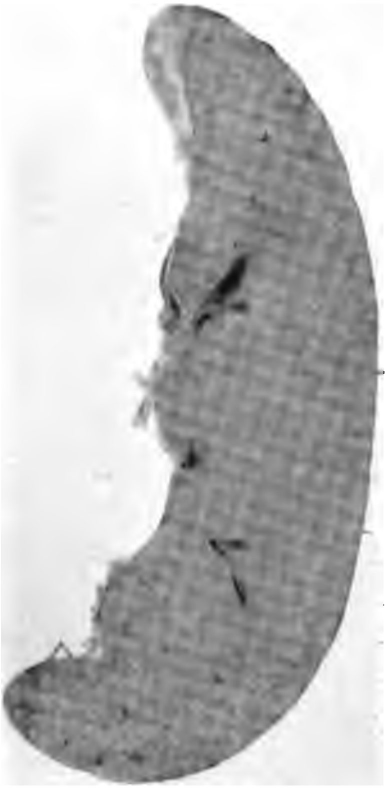


Fig. 171.—Case No. 4. Splenic anemia—late Gaucher type (splenic section mottled).

either of the other 2 cases of the class. This patient was quite well when last heard from, two and one-half years after the removal of her spleen.

The spleen from the third case (Fig. 173) in this class, No. 5, is made up microscopically almost wholly of large spaces—apparently dilated venous sinuses—filled with what in most of them is a homogeneous colloid mass (Fig. 174). In some of the sinuses, however, remains of cellular elements can be made out, while in a few these elements are still plainly shown to be endothelial cells (Fig. 175). Surrounding these distended colloid-filled sinuses are broad bands of fibrous connective tissue, containing here and there remains of lymphoid elements and not presenting the contracted appearance of the fibrous connective tissue in Case No. 4. The most reasonable interpretation of the pathologic process in this spleen is that of a primary endothelial proliferation, a secondary

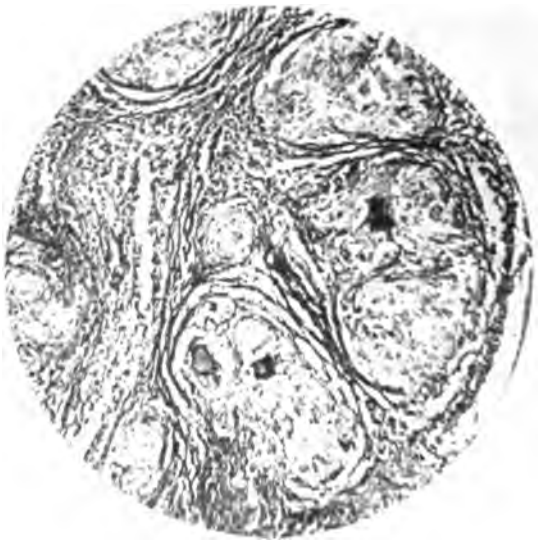


Fig. 172.—Case No. 4. Splenic anemia—Gaucher type (splenic section × 100). Beginning degree of proliferated endothelium, giant-cells, and fibrosis.

connective-tissue increase, and a colloid degeneration of the endothelium.

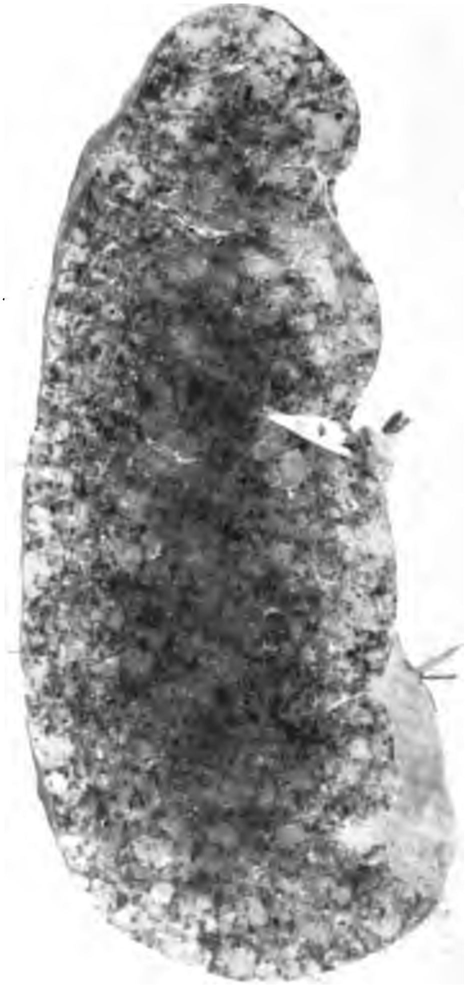


Fig. 173.—Case No. 5. Splenic anemia—late Gaucher type (splenic section mottled. Colloid degeneration and advanced fibrosis).

While, so far as I am aware, no other observer has reported so extensive a colloid degeneration in a spleen of the Gaucher type, it

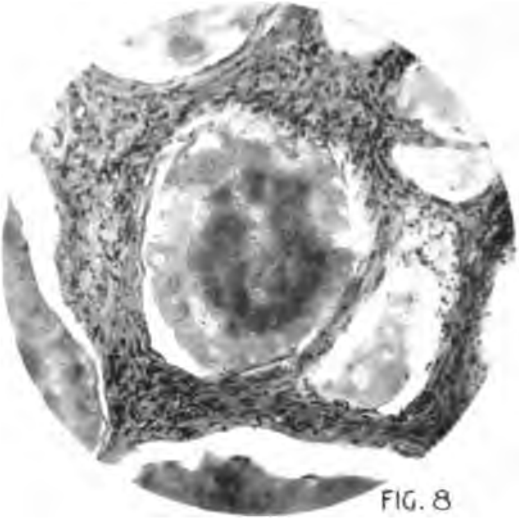


FIG. 8

Fig. 174.—Case No. 5. Splenic anemia—late Gaucher type (splenic section × 100. **Colloid degeneration**).

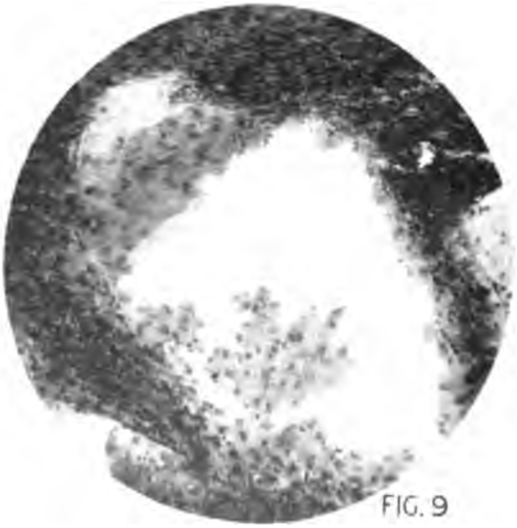


FIG. 9

Fig. 175.—Case No. 5. Splenic anemia—late Gaucher type (splenic section × 100. **Endothelial remains**).

is probable that Marchand's[25] case was in a beginning stage of the same process, since Marchand notes particularly the peculiar homogeneous hyaline appearance of many of the cells. It is possible, also, that the fine linear markings on the endothelial cells, to which attention was first called by Mandelbaum and Libman,[12] and which were to be made out in all 3 of our cases, may mark early stages in the process of degeneration in these structures.

Weichselbaum's[1] case of "primary multiple endothelial sarcoma of the spleen" was the first case of this type to find its way into the literature. Though Weichselbaum omits all clinical data from the report of his case, his description of the morbid histology leaves little doubt as to the character of the lesion. Gaucher[2] next described a case as "splenomegalie primitive—epithelioma primitive de la rate." Williamson's[3] case showed considerable fibrosis of the spleen, with "enormous numbers of large nucleated cells each containing 6 to 10 red blood-corpuscles" in the venous sinuses. Williamson's description is not as full as one could wish, and there remains considerable doubt whether or not his case was of this type. Collier[4] described the histologic changes in the spleen of a case as an endothelioma. His specimens, however, were reviewed by the "Morbid Growths Committee" of the London Pathological Society, who noted the enormous number of endothelial cells, but thought the condition was not an endothelioma. Picou and Ramond[5] next described the lesions in the spleen from a case on which a successful splenectomy had been performed (the first in this group of cases). Bovaird's[9] cases were the first reported in America, and his thorough description of the pathology left little to be added by later observers. He was convinced that the essential lesion was an endothelial hyperplasia and not a neoplasm. Following Bovaird, Harris and Herzog[10] reported the first successfully operated case in America, and coincided with Bovaird that the chief histologic change was an endothelial hyperplasia. The spleen in Rolleston's[13] case showed marked fibrosis and extensive endothelial proliferation. Stengel's[17] case, that of a negro who had had more or less pain in the left side of the abdomen for many years, and on whom splenectomy was successfully performed by Dr. Clark, presented a spleen whose surface was covered with numerous nodules from 1 to 3 cm. in diameter. Histologically, there was enormous increase of the endothelium and fibrous connective tissue. There were many giant-cells, and the endothelium so infiltrated the connective tissue that Stengel was convinced the condition was a true endothelioma. Histologically, this case is apparently an exact counterpart of our case No. 4. Springthorp and Stirling[19] reported 6 cases in one family, on one of whom a successful splenectomy was performed. They describe the morbid histology in the spleen as "a great increase of the fibrillar framework of the spleen pulp made up of anastomosing processes of endothelial cells with their rounded or elongated nuclei." The spleen in Umber's[20] case showed numerous deposits of pigment; the venous sinuses filled with blood and many large mononuclear cells with fine pigment-granules, and many giant-cells in the Malpighian bodies. Mandelbaum and Libman[21], [31] have made thorough pathologic reports on two cases studied clinically by Brill. They were the first[21] to call attention to the peculiar linear markings to be seen with high power on the endothelial cells. They were also the first to call attention to the endothelial hyperplasia in the bone-marrow. In their last report,[31] following the suggestion of Schlagenhaufer[24] and Marchand,[25] they concede that the large endothelial-like cells may arise from the normal endothelium or from normal reticulum. Judging from the cuts illustrating Mandelbaum and Libman's articles, the endothelial cells are much more closely packed than in our Case 3, while the connective-tissue increase is not as great as in our Cases 4 and 5. O'Malley and O'Malley[22] report their studies on the spleen of a case which had been operated on, and describe an endothelial proliferation and a marked connective-tissue hyperplasia throughout the spleen. Schlagenhaufer's[24] case, like that of Gaucher, was complicated with tuberculosis. He concludes that the disease is a general one of the lymphohematopoietic system, and thinks it is analogous to lymphosarcoma. He doubts the endothelial character of the large cells filling the venous sinuses, and suggests that they may be derived from the reticulum. Marchand,[25] in the examination of the spleen from one case, notes especially the hyaline appearance of the endothelial cells, saying that it suggests an amyloid degeneration. He is in doubt as to the origin of these cells, but says they may arise either from the endothelium or from the reticulum.

Krompecher and von Herczel,[23] in the study of one case, conclude that the spleen was the seat of an inflammatory process or a benign new-growth and are inclined to the latter opinion. de Jong and Van Heukelom,[35] in the study of a spleen from a patient who recovered after operation, decided that the cells in the venous sinuses had arisen from the reticulum, though they note that the possibility of an endothelial origin cannot be denied. The liver in their case continued to enlarge after splenectomy, and they attribute this to a proliferation of the cells previously carried there from the spleen, though, of course, this is speculative. Rettig,[32] Risel,[33] and Plehn[34] have also contributed to the literature of this type of splenomegaly. The most recent report is by Mandelbaum,[38] who reports a case of a boy, four and one-half years old, who died the next day after splenectomy. The spleen weighed 490 grams. Autopsy showed the liver and all mesenteric and retroperitoneal lymph-nodes enlarged. After a careful study of the histology of this case Mandelbaum concludes: "It is impossible to deny that a close relation exists between the reticulum and the large cells, even though one cannot find evidences of transition stages between them."

From my review of the cases presented in the literature, and a careful study of the spleens from our own 3 cases, it seems to me that our best interpretation of the histologic pictures presented is that of a primary endothelial proliferation with a secondary proliferation of fibrous connective tissue, and ultimately a degeneration of the endothelium with contraction of the connective tissue. The survey of all the cases suggests a close analogy in their histology with what one meets with in hyperplasias of the thyroid and of the prostate, namely, an initial hyperplasia of the parenchyma filling the acini, a secondary increase of the stroma, and ultimately a degeneration of the parenchyma, with contraction of the connective tissue.

With relation to the origin of the large endothelial-like cells, they appear to me to be much more likely to have risen from the endothelium than from the reticulum. In this connection, it may not be amiss to recall that, though embryologically, the spleen arises entirely from the mesoderm, yet soon after the first appearance of the splenic anlage, as a thickening of the dorsomesogastrium, the celomic epithelium covering it becomes arranged in multiple layers, the deeper ones of which change to mesenchymal type and become scattered throughout the spleen.

It seems to me unfortunate that the trend of medical thought was originally directed toward the consideration of these endothelial proliferations as true neoplasms, with the associated dread of malignancy, since it has no doubt influenced surgeons from hazarding splenectomy; though, of the 9 cases which have been operated on, as reported in the literature, 4 have recovered, while the remaining 5 were in bad condition before coming to operation.

Class C.—Primary (Chronic) Diffuse Hyperplasia of the Spleen (Chronic Splenitis).—In this pathologic class are found 13 of our cases (Nos. 6 to 18). The spleens are all large, weighing from 425 grams (two and one-half times normal) to 1670 grams (nine times normal), with an average of 1089 grams (six times normal). The external surface of these spleens varies in roughness directly in proportion to the development of connective tissue within the organ. On gross section, all of them show more or less fibrosis with dilated vessels. Microscopically, there is a diffuse overgrowth of all the tissue elements, lymphoid, endothelial, and fibrous (Fig. 176). In several the lymphoid tissue is markedly increased, in most the connective-tissue increase is very prominent, and in almost all there is some proliferation of the endothelium of the venous sinuses. In all the cases with marked connective-tissue overgrowth there is more or less sclerosis and atrophy of the pulp and Malpighian bodies. The latter frequently also show some hyaline degeneration. In several of the cases (Fig. 177) in which the fibrosis is most marked dilatation of the capillaries and arteriosclerosis

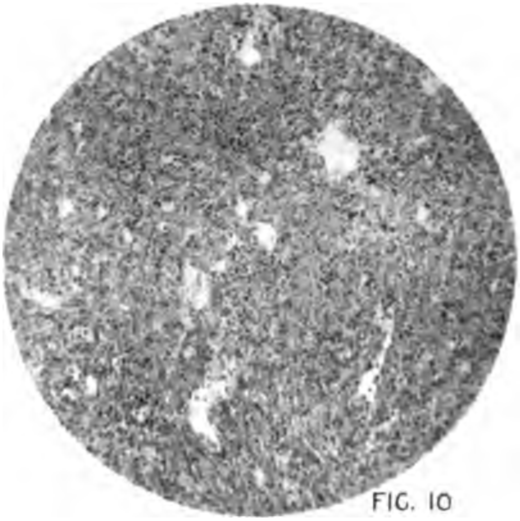


FIG. 10

Fig. 176.—Case No. 13. Splenic anemia (splenic section × 100. Chronic diffuse hyperplasia).

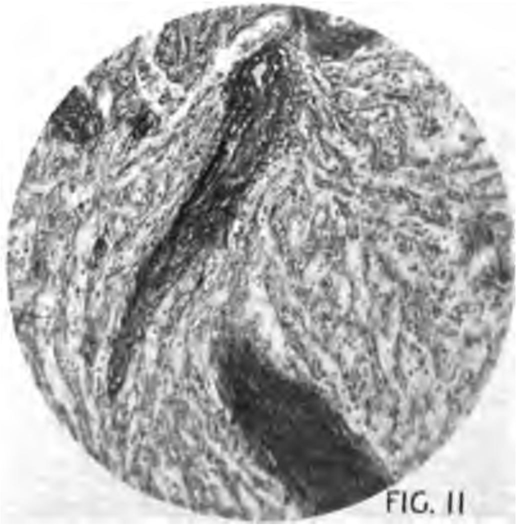


FIG. 11

Fig. 177.—Case No. 8. Splenic anemia, with Banti's syndrome (splenic section × 100. Dilated capillaries and fibrosis).

are also present. This process is especially marked in three cases which presented clinically the syndrome of Banti's disease and showed cirrhosis of the liver at operation. The pathology of this type of primary splenic anemia has been so well described by Banti,[6] Sippy,[7] Osler,[8, 36] Wentworth,[11] Warthin,[16] Marchand,[15] Simonds,[26] Lyon,[27] and others that further description is unnecessary. The picture is that of primary chronic diffuse parenchymatous and interstitial inflammation. Whether this process is the result of a local micro-organismal invasion or of a locally acting toxin is undetermined, though hypothetically the latter is the more probable.

Group II.—Cases with a Doubtful Clinical Diagnosis Falling between Splenic Anemia and—(a) *Infection;* (b) *Pernicious Anemia; or* (c) *Hepatic Cirrhosis.*—In this clinical group are 4 cases (Nos. 19, 20, 21, and 22) on whom splenectomy was done, and one autopsy case, No. 23; and yet in whose histories the element of infection was so prominent as to make doubtful the clinical diagnosis. The spleens in these cases, while enlarged, are relatively smaller than those in the preceding group, ranging from 320 grams (two times normal) to 1340 grams (eight times normal), with an average of 800 grams (four and one-half times normal).

In one of these cases, No. 19, the spleen, which weighed only 320 grams, shows only an increase of the parenchyma without endothelial or connective-tissue proliferation. In this case not only were the clinical data insufficient on which to base the diagnosis of splenic anemia, but the pathologic picture was also not that of the other clinically well-defined members of the group. The patient, however, is alive and well about two years after operation.

In Case 20 the spleen, weighing 640 grams, was soft and showed an increased parenchyma and some increase of connective tissue. There was evidence of old and recent hemorrhage in the numerous infarcts and areas of blood-pigment. This case presented clinically a wide-spread infection of the upper abdomen, and there is little in the pathologic picture of the spleen to suggest its relationship to splenic anemia. The patient died about six months after operation, with symptoms of nephritis and general infection.

In Case 21 the spleen weighed 900 grams, with a rough, nodular exterior and showed on section dilated vessels and marked fibrosis. Microscopically the fibrosis was found to be quite diffuse, the lymphoid elements proliferated, and there was also some proliferation of the endothelium of the venous sinuses. This case was complicated clinically with a doubtful history of tuberculosis and syphilis. Pathologically, one could not distinguish it from members of Group I, clinically splenic anemia. The patient died, two months after operation, of nephritis complicated by pleurisy with effusion.

Case 22 had had Raynaud's disease five years before operation, and gall-stones were found at operation, at which time also a 1340-gram spleen was removed. The surface was rough, hard, nodular, and on section showed a marked fibrosis. Microscopically, the fibrous overgrowth is found to be diffuse, the venous sinuses shrunken, with no endothelial proliferation, and there is no marked hyperplasia of the lymphoid elements.

Case 23 was a male, twenty-five years of age, who had been sick for two years. At the time he was examined, a few weeks before his death, he presented an enlarged spleen with a red blood-count of 2,900,000, a leukocyte count of 5200, and hemoglobin of 67 per cent. Later his leukocyte count went up to 13,000. His color-index was always 1 or above. This patient came to autopsy without operation, through an intercurrent lobar pneumonia. Aside from the pneumonia, the liver was found slightly enlarged and fatty, and there was some chronic nephritis. The spleen weighed 1160 grams (six times normal). It was smooth, mottled on gross section, firm, and fibrous. Microscopically, there is a very marked fibrosis and the venous sinuses are dilated, but without any marked proliferation of the endothelium.

In the list of cases with a doubtful clinical diagnosis of splenic anemia are two which a fuller clinical review seems to place in a group of atypical pernicious anemias. The first of these, Case 24, was a male, aged twenty-seven years. Splenectomy February 9, 1910. The spleen weighed 1640 grams. It was smooth, evenly marked, showed but a slight increase of fibrous connective tissue, but an enormous amount of blood-pigment and débris of broken-down blood-cells. The patient died six months later without any material interruption having been made in his chain of symptoms by the operation. The pathologic findings in this case suggest pernicious anemia.

Case 25, on whom a doubtful clinical diagnosis of splenic anemia or pernicious anemia was made, was that of a child ten years of age, who was in a moribund condition when brought to the hospital, and who died two days later without operation. His blood-picture presented some of the characteristics of pernicious anemia (red blood-corpuscles, 1,013,000; leukocytes, 13,000; normoblasts, megaloblasts, myelocytes, and marked poikilocytosis; hemoglobin, 15 per cent.), and there had been recurrent hemorrhages from the bowels for a year. At autopsy, aside from small areas of submucous hemorrhage throughout both large and small intestines, the only pathologic condition found was a spleen three times normal size, pale, hard, and fibrous, and a much enlarged liver which was light in color and soft. Histologically, the spleen showed a thickened capsule with advanced fibrosis, and almost entire absence of lymphoid elements. When stained for iron, neither spleen nor liver showed the deposit so common in cases of pernicious anemia.

Case 26 was a female twenty years of age on whom a doubtful clinical diagnosis of splenic anemia was made. At operation, February 26, 1912, the surgeon made a diagnosis of probable primary cirrhosis of the liver. A spleen weighing 750 grams was removed. The patient died two months after operation.

Group III.—Cases of Splenectomy for Conditions Other than Splenic Anemia.—Case 27 was a female, aged twenty-nine years, on whom a clinical diagnosis of painful wandering spleen was made. Splenectomy was performed January 22, 1912. A spleen weighing 170 grams and apparently normal in all respects was removed.

Case 28 was a female, aged twenty-nine years, on whom a clinical diagnosis of painful wandering spleen was made. Splenectomy was performed June 27, 1908. The spleen weighed 145 grams and showed a somewhat atrophied parenchyma, but was otherwise normal.

Splenectomy was done in both of the above cases for the relief of pain, and was successful in both.

It will thus be seen, from this brief description of the above 11 cases, that 3 (Nos. 21, 23, and 25) which were clinically doubtful splenic anemias were indistinguishable pathologically from those cases in which the clinical diagnoses were positive. However, Case 21 gave a doubtful history of associated tuberculosis, Case 23 of an intercurrent infection (pneumonia), and Case 25 was a child and practically moribund when first examined at this clinic.

General Summary

1. Pathologic study of 18 spleens removed at operation in the Mayo Clinic from November 14, 1905, to November 1, 1912, from patients on whom positive clinical diagnoses of splenic anemia had been made, shows that in each spleen there was hyperplasia of one or more of the constituent tissue elements. In two spleens the lymphoid tissue was so markedly overgrown as to suggest a diagnosis in one of lymphoma and in the other of lymphosarcoma. In three spleens the proliferation of the endothelium of the venous sinuses was most predominant. In 13 spleens the process was a chronic diffuse one, involving all tissue elements.

2. While any case of primary splenomegaly may begin as an overgrowth of the lymphoid tissue or of the endothelium, in the ordinary course of events a secondary overgrowth of the stroma of the gland will later appear, accompanied by degeneration of the lymphoid or endothelial elements.

3. The largest spleens are those in which the lymphoid or endothelial hyperplasia is greatest. As the connective tissue overgrows, the spleen may be reduced in size, owing to reduction in the amount of the lymphoid and endothelial elements.

4. The roughness of the exterior of the spleen is in direct proportion to the development of connective tissue within it.

5. In primary splenomegaly a secondary cirrhosis of the liver is associated with great connective-tissue overgrowth and degeneration of the pulp of the spleen.

6. From what we know of hyperplasias in other organs, it would

seem unnecessary to assume hypothetically the presence of three different causes for the production of the three primary histologic types of splenic anemia.

7. The histopathologic picture presented in all three types of spleens from cases of primary splenic anemia seems to be in complete harmony with the hypothesis of the presence of a slowly acting local toxin.

8. There are certainly spleens from clinically doubtful cases of splenic anemia which the pathologist cannot distinguish from the spleens from clinically undoubted cases. Yet it must be conceded that the finding of a great hyperplasia of one or all the tissue elements of the spleen, without other diagnostic lesions elsewhere in the body, is strong corroborative evidence of the clinical diagnosis of splenic anemia.

In conclusion I wish to thank Franz Wildner, of this laboratory, for the use of sections from some of the cases, prepared under his careful direction, and which will be more fully described by him in an early forthcoming article on certain features of the pathology of the spleen. I am also under obligations to H. Z. Giffin for the clinical notes which he has so kindly supplied.

REFERENCES

1. Weichselbaum: "Virchow's Archiv," 1881, vol. lxxxv, p. 562.
2. Gaucher: "Thèse de Paris," 1882; "Semaine Méd.," 1892, vol. xii, p. 331.
3. Williamson: "Med. Chron.," Manchester, 1893, vol. xviii, p. 103.
4. Collier: "Trans. Path. Soc.," London, 1895, vol. xlvi, p. 148.
5. Picou et Ramond: "Arch. de Méd. Exp.," 1896, vol. viii, p. 168.
6. Banti: "Beiträge z. path. Anat.," 1898, vol. xxiv, p. 21.
7. Sippy: "Amer. Jour. Med. Sci.," 1889, vol. cxviii, pp. 428–442, 570–586.
8. Osler: *Ibid.*, 1900, vol. cxix, p. 54.
9. Bovaird: *Ibid.*, 1900, vol. cxx, pp. 377–402.
10. Harris and Herzog: "Ann. Surg.," Philadelphia, 1901, vol. xxxiv, pp. 111–134.
11. Wentworth: "Boston Med. and Surg. Jour.," 1901.
12. Brill: "Amer. Jour. Med. Sci.," 1901, vol. cxxi.
13. Rolleston: "Clinical Jour.," 1902, vol. xix, p. 401; "Brit. Med. Jour.," 1903, vol. ii, p. 573.
14. Warthin: "Contrib. to Med. Res.," dedicated to V. C. Vaughn, Ann Arbor, Mich., 1903, pp. 216–236.
15. Marchand: "Münch. med. Woch.," 1903.
16. Dock and Warthin: "Amer. Jour. Med. Sci.," 1904, vol. cxxvii, pp. 24–55.
17. Stengel: "Amer. Jour. Med. Sci.," 1904, vol. cxxviii, pp. 497–533.
18. Jepson and Albert: "Ann. Surg.," 1904, vol. xl, pp. 80–97.
19. Springthorp and Stirling: "London Lancet," 1904, vol. ii, p. 1013.
20. Umber: "Zeit. f. klin. Med.," 1904, vol. lv, p. 289.

21. Brill, Mandlebaum, and Libman: "Amer. Jour. Med. Sci.," 1905, vol. cxxix, pp. 491–504.
22. O'Malley and O'Malley: "Amer. Jour. Med. Sci.," 1905, vol. cxxix, pp. 996–1009.
23. Krompecher u. von Herczel: "Wien. klin. Woch.," 1907, No. 5, p. 127.
24. Schlagenhaufer: "Virchow's Archiv," 1907, vol. clxxxvii, pp. 125–163
25. Marchand: "Münch. med. Woch.," 1907, vol. liv, No. 1, pp. 1102, 1103.
26. Simonds: "Jour. Infect. Dis.," 1908, vol. v, pp. 23–45.
27. Lyon: "Osler's Modern Med.," 1908, vol. iv, pp. 735–778.
28. Cabot: "Osler's Modern Med.," 1908, vol. iv. pp. 595–680.
29. Adami: "Principles of Path.," 1908, vol. ii, pp. 221–231.
30. Lewis: "Trans. Assoc. Amer. Phys.," 1908, vol. xxiii, p. 165.
31. Brill, Mandlebaum, and Libman: "Amer. Jour. Med. Sci.," 1909, vol. cxxvii, pp. 849–857.
32. Rettig: "Berlin. klin. Woch.," 1909, vol. xlvi.
33. Risel: "Ziegler's Beit.," 1909, vol. xlvi, p. 241.
34. Plehn: "Deut. med. Woch., 1909, vol. xl, p. 1749.
35. Josselin de Jong and Van Heukelom: "Ziegler's Beit.," 1910, vol. xlvii, pp. 598–629.
36. Osler: "Principles of Practice," 1912, pp. 885–888.
37. Downey and Weidenreich: "Arch. f. mik. Anat.," 1912, vol. lxxx, Abt. 1, pp. 306–395.
38. Mandlebaum: Jour. Exper. Med., 1912, vol. xvi, pp. 797–821.

FACTORS OF SAFETY IN OPERATING FOR EXOPHTHALMIC GOITER*

CHARLES H. MAYO

The remarkable progress which has been made during the past twenty years in the surgical treatment of Graves' disease is worthy of comment. This progress is due to a greatly increased knowledge of the disease, and has resulted in a reduction of the mortality, in a greater number of cures, or in greatly lessened disability.

In the early nineties the disease was considered from a purely medical point of view, and very often patients were nearly moribund before surgical aid was given. It has been shown, however, that the disease is chronic and that there are conditions and periods of activity peculiar to it which should be treated medically in preparation for an operation later, unless the improvement be continuous and the recovery complete.

DIAGNOSIS

Because of the severe symptoms which present themselves the majority of cases of exophthalmic goiter can be readily diagnosed as such, but there may be a small number in which the diagnosis is made with difficulty. Most cases in which there is doubt are, in all probability, not true cases of Graves' disease, the symptoms being due to myocarditis, certain forms of nephritis, and some obscure nervous manifestations, the causes of which are, as yet, unknown.

Kocher believes that cases of Graves' disease which are difficult to diagnose should be accepted as such only if they show the blood-changes commonly found in acute or active Graves' disease. From an observation of several hundred cases of exophthalmic goiter, Plummer* has shown that the disease runs a fairly regular course.

---

* Reprinted from the "Jour. Amer. Med. Assoc.," July 6, 1912, vol. lix, pp. 27.

There is usually more dilatation of the heart and the symptoms are more acute in the first period; they assume a chronic type in the second. It is well known, however, that a few cases run their course to death within a few weeks, while others have only the most temporary remission, growing progressively worse for a few years, ending in death, as a rule. It must be recognized, also, that cases of single or multiple adenomas of the thyroid may undergo a degeneration which acts on the system somewhat like the acute toxemia of hyperthyroidism, causing dilatation of the heart, nephritis, and general anasarca. Nervousness, tremor, and tachycardia may be present. Protrusion of the eyes does not occur in these cases, but the myocardial change may cause a widening of the palpebral fissure, or Dalrymple's sign. These cases, often called Graves' disease, should be classed as complicated simple goiter, the mortality of operation being fully equal to that of operations in the active and severe types of Graves' disease.

The mortality from operations performed during this early period by surgeons of considerable experience was from 20 to 30 per cent. Our mortality (W. J. and C. H. Mayo) in the first sixteen cases was 25 per cent. Many of these patients were suffering from advanced myocardial changes, degeneration of the liver and kidneys, so that cure was out of the question, and checking the toxemia with relief of symptoms was all that could be hoped for. The relief of those who survived the operation, however, was so immediate and remarkable that the new patients were often advised to operation by the old. The high mortality, which should and would have been medical with a little more delay, was shifted on to the surgical side, and, like a vicious circle, the higher the mortality, the greater the delay, and vice versâ.

---

* "If the average course of the disease be represented by a curve, the greatest height of the intoxication is found to be reached during the latter half of the first year and then rapidly drops to the twelfth month. In many instances it reaches the normal base-line during the next six months; more often it fluctuates with periods of exacerbation for the next two to four years. Secondary symptoms and exophthalmos may remain, but the active course rarely continues over four years without distinct intermissions. The ascent may be gradual, sudden, or irregularly marked by many secondary curves."

It was not until the beginning of the present century that the experience gained by the early workers in this field bore fruit. The disease became rather generally considered as surgical even by some physicians with a large experience in the medical treatment of simple goiters.

That factors of safety are gradually becoming recognized is proved by the present mortality following surgical operations, which is a varying one—from 1 to 4 per cent. The estimated proportion of cures, based on the examination of patients operated on and from letters and reports, is about 75 per cent. These patients have been restored to usefulness, resuming former occupations, and are free from nearly all former symptoms. Some of the patients with extreme and long-continued exophthalmos may still show symptoms of this condition, but which cause no discomfort; others may occasionally have tachycardia, and a few may have an occasional relapse of the general nervousness. It must be admitted, too, that if there be an increase in the size of the remaining portion of the gland, a small number of patients will have a partial relapse of all symptoms after being practically well for a long period of time. Should a patient under medical treatment relapse after a period of improvement, the treatment is renewed. Should there be a relapse after surgical treatment, because of too little gland removed, or an increase of the remaining portion, it does not indicate a failure in the surgical principle, but calls for further operation.

Within the past year we have operated, between deaths, on a consecutive series of 278 cases of exophthalmic goiter. This is a decidedly marked gain over our early work, and I believe it has been caused by taking advantage of the so-called "factors of safety" in the treatment, preparation, and operation of these patients.

1. As regards operating during periods of exacerbation or excessive activity of the disease: The mortality in these cases is fre-

quently high, and it is such we would choose for medical treatment, *i. e.*, rest, *x*-ray, etc., with attention to the heart, stomach, and intestines according to the indications presented by the individual case, until the exacerbation of symptoms subsides.

2. Gastric crises and acute delirium are serious manifestations and operation should not be done until the conditions have subsided; the cases, until then, remain medical.

3. Dilatation of the heart which exceeds 1 inch is a serious condition, while that of an inch and a half will give a percentage of unavoidable mortality for the radical operation of thyroidectomy. The line of treatment is, therefore, indicated.

4. Ligation as a method of surgical treatment was practised in the early part of the last century and again recommended by Wölfler and others in the latter part of the same century. The method now has an accredited position in the treatment of exophthalmic goiter. Patients seen in the early stages are sometimes wonderfully improved by the simple operation of double ligation. These cases are, however, comparatively few in number, and, since it is this type which may possibly abort, it is difficult to say that the improvement in all cases necessarily comes from the operation.

5. Serious risks are treated by a single ligation of the vessels at the upper left pole. The reaction is about three-fourths as severe as from a double ligation, but the missing one-fourth is an element of safety. If the reaction be very severe, a second ligation of the right upper pole is made a week later. As compared with the first ligation, the reaction following this one is slight. If the reaction be not severe, at the second operation the right lobe, isthmus, and possibly a portion of the left lobe are removed. In some cases of extreme emaciation, yet with a temporary fair or improved condition, a double ligation is made at the one operation. In several hundred patients the average gain in those who were below weight at the time of ligation was 22 pounds within four months. At this time a thyroidectomy of one-half or three-fourths of the gland can be made with small risk.

Ligation of vessels should be made close to, or should include some of, the pole itself, so that a reversal of circulation in anastomotic branches with the inferior artery may not occur. Thyroidectomy of three-fifths or more of the gland is indicated in most of the chronic cases in which dilatation of the heart does not exceed one inch and there are no complications—ascites or mental changes.

The small percentage of patients with exophthalmic goiter who relapse in from one to several years after partial thyroidectomy, with an increase in the size of the remaining lobe, should have the benefit of further surgical aid. Unless medical treatment be rapidly beneficial in such cases, the primary procedure should be ligation of the vessels at the superior pole, leaving only the inferior artery and the lateral and inferior veins. Should this operation not restore these patients to their former improved condition, a part of the gland can be excised at a later period with but little risk.

Ether, preceded by atropin and morphin, is the anesthetic of choice for double ligations and thyroidectomy. If there be extreme nervousness, scopolamin is used, and the worst type of cases with affections of the heart and kidneys are operated on by local anesthesia or receive the benefit of Crile's anocia preparation—injecting local anesthesia into the field of operation in addition to the other preparations before ether is administered.

Ligations, both single and double, in the worst types of Graves' disease have been followed by a mortality which has fully equaled or exceeded the mortality of thyroidectomy. In the 278 operations there were 105 single and 13 double ligations.

EXOPHTHALMIC GOITER

Single ligation	105
Double ligation	13
Single ligation followed by thyroidectomy	30
Two single ligations followed by thyroidectomy	21
Double ligation followed by thyroidectomy	26
Thyroidectomy	78
Thyroidectomy followed by ligation	4
Thyroidectomy followed by ligation followed by thyroidectomy	1
Total	278

GOITER*

CHARLES H. MAYO

The development and structure of the body have always been a most interesting study, and it has become a most fascinating one since our advancing knowledge of the former "wonder glands" of the body shows that they are the real architects and builders and that they control many of the most important functions of the body. When this knowledge was first acquired, to each gland was attributed an exact and sole duty, but it is now known that the functions of these glands, especially those of the ductless group, are intimately correlated. They each have a great preponderance of control over certain functions, causing typical disease when one is deranged or absent, and atypical disease when a derangement in function of possibly two or more of the associated glands occurs. All the animals are supplied with these controlling bodies in some form, and, while the substance of the gland remains the same in character, the location and presence of the capsule vary somewhat.

In the human being the thyroid is of utmost importance, and the first bud of its development can be seen in the human embryo of 4 mm. Formerly supposed to develop from three anlages, it is now known to be wholly formed from the median one, originating between the three divisions of the tongue, from which point it descends in the neck to its resting-place astride the anterior upper trachea. It consists of two lateral lobes and an isthmus. Anomalies are caused by failure of the gland to develop, by its continuing its fetal form as permanent structure, by failure to leave its original location (as lingual thyroid), by portions breaking off in the descent (attached or completely carried away), thus causing accessory or aberrant thyroid, or the rather common occurrence of becoming entangled in the developing hyoid bone, stringing out a portion of the gland known as the pyramidal lobe. Sometimes, though rarely, pharyngeal embryonic mucosa is drawn down in the line of descent, causing the so-called thyroglossal duct cyst. Because of the disappearance of the thyroglossal duct, which occurs in the early development in the human being, it was believed that this gland in some less developed animal life delivered through a duct, like the submaxillary gland, and, long looked for, was finally found by Gaskell. In his search for the highest form of development in invertebrate animals he shows that this surface delivery does occur in some of them, such as the limulus, sea-scorpion, king crab, ammocetes, *et al.* As has been suggested by MacCarty, the best place for the further study of this gland is in this type of animal, although singularly enough in them it delivers into the genital tract. The next advance in our knowledge will come through finding the animal invertebrate or vertebrate in which the duct disappears.

---

* Read before the Chicago Medical Society, October 31, 1912. Reprinted from the "Illinois Med. Jour.," February, 1913, pp. 125-136.

We can readily see that the structure of this gland is most important when we consider that its blood-supply arises from approximately the same sources as the vessels supplying the circle of Willis, and that its vascular area is the same as that for the brain. Under certain conditions of thyroid activity the vessels supplying it enlarge considerably. The secretion of the gland is in the nature of an iodothyroglobulin.

The mother's thyroid undoubtedly influences the growth of the child in utero. A babe without functionating thyroid at birth appears normal and the failure of this function requires several months to make itself manifest. When thyroid is fed to those deficient of it through birth, operation, or disease, it improves their condition. We can more readily understand its relation as an associated sex gland in the higher animals and human beings from the genital tract position of the thyroid in the higher invertebrates. This is noticeable in the goiters of adolescence and lesser enlargements which are so common at puberty when the ovaries and uterus take on development, in the slight increase in size through congestion preceding menstruation which is so often noted, in the frequent thyroid symptoms during the early months of pregnancy due to extra demands upon its secretion, and in the symptoms of varying hyper- and hypo-function seen at the menopause. Again we not infrequently see a lessened catamenia with an increase in weight and sterility between the ages of twenty-five and forty, which is often apparently due to a decreased activity of the thyroid. In such cases thyroid feeding at times seems to improve their condition.

It may be said that these statements are but clinical observations. They do, however, offer a most inviting field for investigation in order that we may be supplied with more accurate knowledge.

In the human being the gland weighs from one to one and one-half ounces. There is, however, a large factor of safety provided in all these structures which would indicate that a portion of the gland, stated as probably one-sixth, would be sufficient to furnish the necessary secretion. There is a wide variation in the structure of the ductless glands, due to failure to completely develop, and to various forms of degeneration which occur after development has been completed, without sickness or symptoms. According to Lorand, the deferring of old age requires the continued presence of some of the thyroid throughout life. The cretin is the child without thyroid from birth. The loss of thyroid in the adult causes myxedema.

It can be readily recognized then that transplantation of the gland from similar beings has become a fruitful field of experimentation. Previous to the antiseptic period transplantations of all sorts were almost impossible, but, through antiseptic and aseptic detail, skin, bone, and conveying structures, such as nerves, have been transplanted. More recently, through better technic, blood-vessels and glands also have been transplanted. Such transplants seem to fulfil their purpose, although the original tissue may no longer exist, but has formed a framework for tissues which permit of a "near-function." In transplanting glands it is at once realized that we are dealing with the highest type of tissue, the next thing to brain-substance. They have a function not unlike the brain, only they transmit their influence by wireless hormones instead of nerves, and while the temporary effect may be marvelous through the hormones of this secretion, its permanency is rarely seen, its benefits lasting only a short time after the disappearance of the structure through phagocytic activity or true degeneration. Usually a necrosis of the center occurs—a degeneration which gradually spreads to the periphery of the transplanted gland. Naturally we would expect but temporary relief in transplanting from one animal to another or to a human being in whom there is a leaking of the blood.

Concerning the etiology of goiter much has been written, but there is little as yet which seems positive; the most commonly accepted theory is that it is a water-borne irritant which acts on the gland. In our own country patients come from every state with every possible differing water-supply and surroundings, as well as elevation.

It is impossible in the human being to describe just what constitutes a strictly "normal" thyroid; there are conditions of the gland which must nearly approach it and wide variations from it which apparently give no symptoms. It is evident that an increased secretion of the gland occurring with increased parenchyma must often be neutralized in the body, as symptoms do not always manifest themselves until some shock or break in the equilibrium of the nervous system renders the condition apparent. It is also evident that less thyroid seems to be necessary in advancing years.

It would appear that the disease is on the increase according to the increasing number of operations that are being made for goiter. It must be remembered, however, that many of these patients have had the goiters from ten to twenty years, so the percentage of operation is greater now than it will be a few years hence. Over 1000 operations for goiter were made at St. Mary's Hospital during the past ten months.

While the thyroid gland is subject to frequent diseases which increase its size, only a small percentage of such enlargements are malignant. Most of them are so-called simple goiters and conform to the normal outline of the gland. Others, however, appear as a rounded tumor growth or as an irregularly developed tumor consisting of an adenoma or of adenomas.

The goiter of adolescence is an edematous condition of the gland due to watery colloid. This type often disappears with or without treatment and seldom requires operation. Iodin is very effective in these cases.

Simple goiter and adenoma through degeneration coming from natural causes or induced by the stimulation of iodin in long-standing goiters may produce the symptoms of a toxemia with attendant effects on the heart, kidneys, and liver. These cases may have all the nervous symptoms and heart complications of a bad case of Basedow's disease without the protruding eyes. Operations on them are fully as serious as in the ordinary case of Graves' disease.

Exophthalmic goiter and hyperthyroidism are terms which have been applied to a disease recognized by a group of varying symptoms which have been described for the past one hundred and fifty years, at first as Morgagni's disease, then Parry's disease, Moebius' disease, later Graves' and then Basedow's disease. It was not until 1885, when Moebius attributed the condition to a derangement of function of the thyroid gland, that a true advance in knowledge was made. As is shown in the pathology of the thyroid, some cases present a general increase in the parenchyma, while in others it is in scattered areas. There is a variation in the nervous system of the individual effected by the hyperactivity of the gland, so one may look for all degrees and stages of this chronic disease which has now, however, become quite generally accepted throughout the world as amenable to surgical treatment.

There is no question but that Graves' disease is a chronic malady and only occasionally runs an acute course to termination. According to Plummer's observations, there seems to be a period of ascent during the first few months before the heart dilates. After this occurs the patient continues in a serious condition until about the end of the first year. During the second year the case can be classed as a chronic one subject to fluctuations. Possibly the most critical period is the few months following the first dilatation of the heart. While the large majority of cases can be easily diagnosed from the nervous symptoms, tachycardia, goiter, and eye symptoms, there are a few cases in which it is difficult to diagnose true hyperthyroidism from pure neurasthenia, myocarditis, or Bright's disease, as well as a few cases in which there may be a complication by affection of the hypophysis, thymus, or adrenals. These cases are not relieved by operation on the thyroid. Rehn, of Frankfurt, believes that the most serious cases are complicated by thymus disease as well. In them he removes this structure if present.

It is our practice not to treat the serious cases as subjects for emergent surgery, but tide them through these temporary exacerbations. In the most severe cases the superior blood-supply is ligated, sometimes in two stages, and later we do a thyroidectomy. The average gain in weight of this group after ligation is 22 pounds during the first four months. A thyroidectomy then becomes a safe procedure.

The anesthetic of choice is ether for general surgical operations. It acts well in simple goiters and also in the majority of cases of hyperthyroidism. By reason of complications, disease of the kidneys, heart, or lungs, tracheal pressure or high blood-pressure, a local anesthetic may be indicated. In some cases it is advisable to secure the benefits of combined anesthesia by the injection of 0.5 per cent. novocain, followed by a light general anesthetic. In using ether it is advisable to give the patient $\frac{1}{120}$ grain of atropin and a small quantity of morphin one hour before the operation. The atropin keeps the pharynx and trachea dry. In very severe cases of hyperthyroidism the giving of $\frac{1}{200}$ grain of scopolamin with $\frac{1}{8}$ grain of morphin does much to quiet the apprehensiveness of the individual.

Operation: In ligating the blood-supply of the gland the vessels of the superior group are chosen because of their accessibility. The inferior thyroid vessels are usually ligated in cases where a serious relapse occurs between the ligation of the superior vessels and the proposed thyroidectomy. The transverse incision across the center of the thyroid cartilage is employed for ligation of the superior vessels, as here there is freedom from the possibility of nerve injury. The anterior border of the sternomastoid muscle is exposed and drawn outward, clearing the outer edge of the omo-

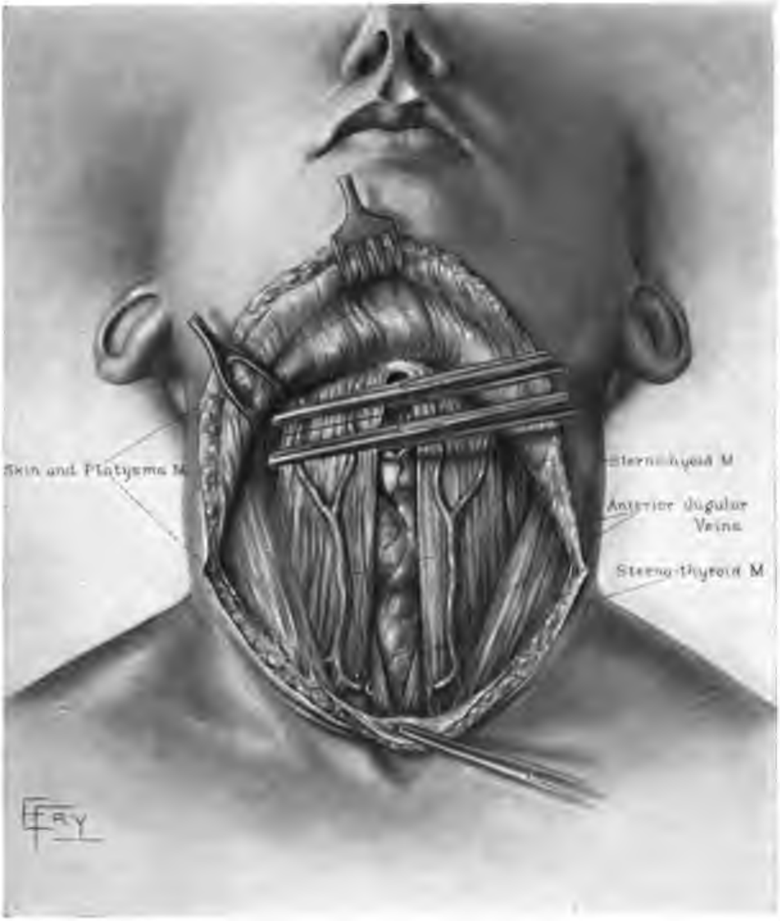


Fig. 178.—Exposure of anterior muscles, cutting of sternohyoid.

hyoid, which is drawn inward. This brings into view the upper pole of the thyroid gland. The ligature is placed at the pole or slightly on the gland. This prevents the reversal of circulation in one of the large branches of anastomosis with the inferior which occurs when the vessel is ligated higher up. One or both sides are ligated at the same time, according to the conditions and the necessities of the case.

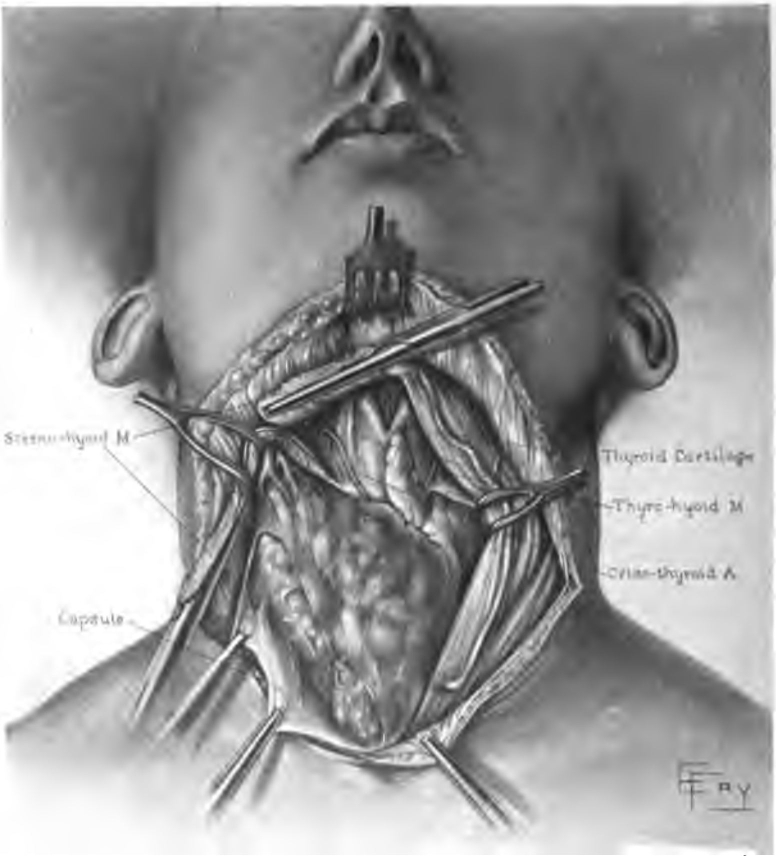


Fig. 179.—Opening lateral thyroid fibrous capsule.

Extirpation of the gland or resection is made by a transverse incision, passing from one external jugular vein to the other in a natural skin-crease low in the neck. The skin and platysma muscle are lifted upward as a single flap, exposing the general outline of the gland, which is now brought into view by dividing vertically between the sternohyoid and thyroid muscles (Fig. 178). The true

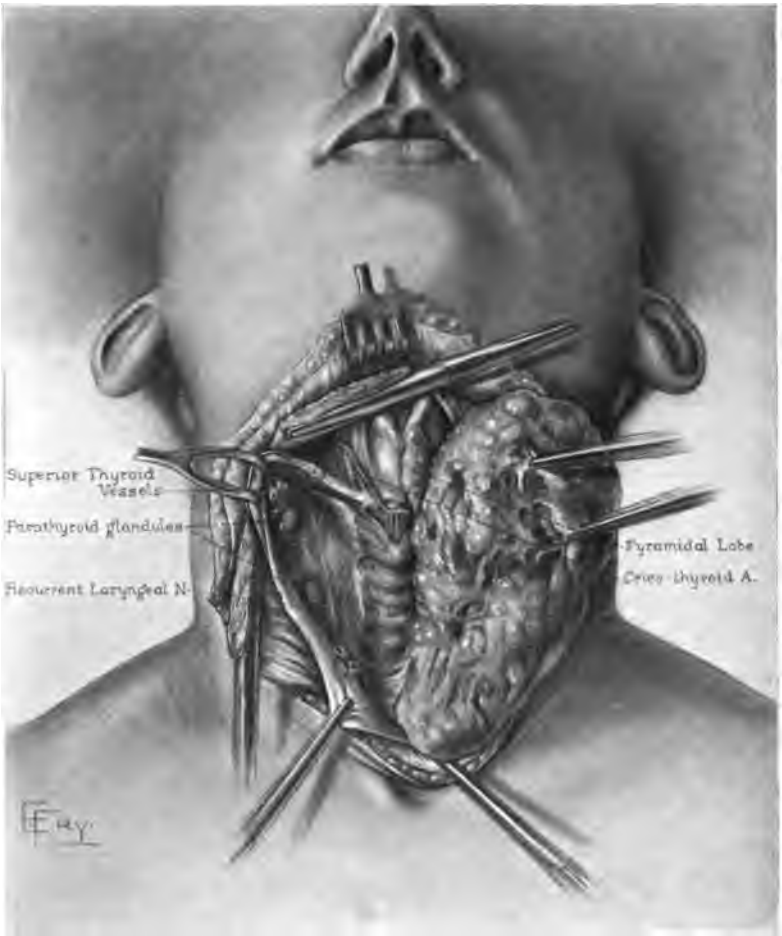


Fig. 180.—Elevation of thyroid gland.

capsule of the gland is recognized as the one containing the blood-vessels; false or fibrous capsules do not have them (Fig. 179). Usually the lobe to be removed can be elevated between these

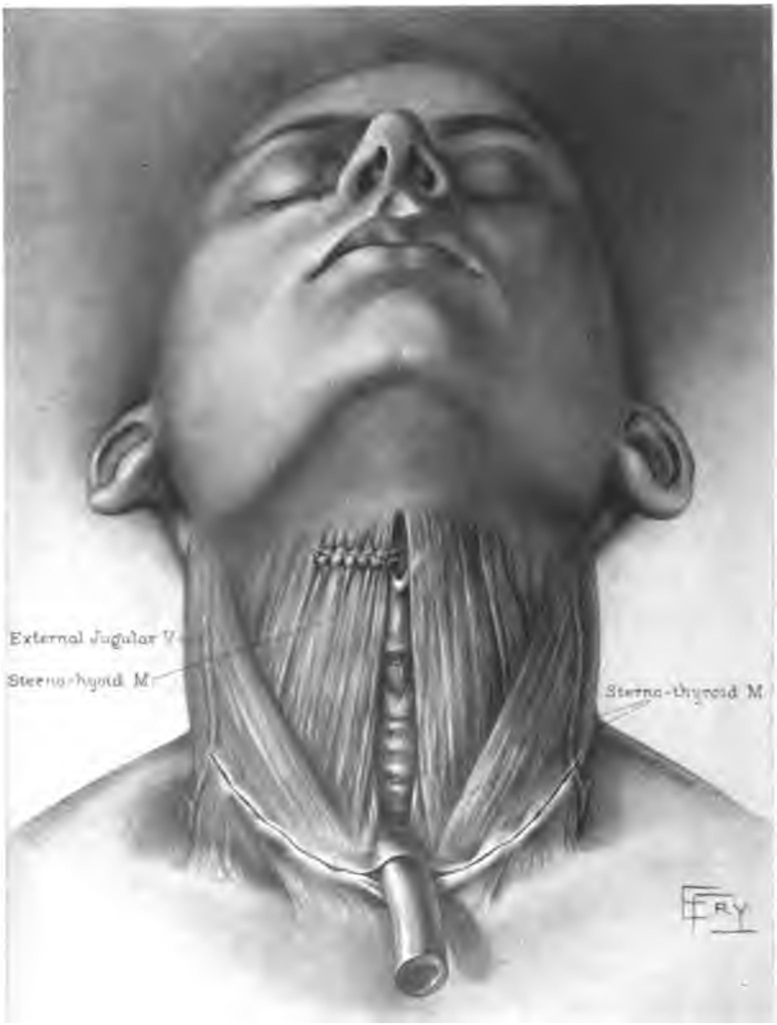


Fig. 181.—Suture of muscles, drainage, and closure of flap.

muscles as they are stretched, but in large goiters and in exophthalmic goiters it becomes necessary to cut the muscles on the one side, rarely on both. They should be cut between two forceps which are placed near the upper part of the muscle, nearly to the top of the skin dissection, as this procedure preserves the body of the muscle with its nerve-supply and breaks the line of penetrating muscle-moved scar so disfiguring after some operations. The lobe to be removed is now elevated and its vessels caught and cut between forceps, many being applied, as all vessels do not need ligating and often several can be caught in one ligature (Fig. 180). This method seems preferable to the immediate application of double ligatures unless the number of forceps which it is necessary to use becomes a hindrance. The high division of muscle gives ready access to the superior thyroid artery, which, after being divided, permits of the rotation of the lobe across the trachea, where it is usually separated at the merging of the isthmus into the left lobe unless it is desired also to remove part of the lobe. In very large goiters causing tracheal pressure it is often advisable to divide the left sternohyoids as well as to free the trachea by dividing the isthmus, the central portion of the gland being removed by turning the lobes outward. This operation is somewhat more bloody, but quite safe, as the trachea is exposed early. Catgut is efficient suture material. Silk is less pleasant to handle (Fig. 181).

Tubular drainage is employed for twenty-four hours, except in large substernal goiters, when the drain is removed within a few hours in order that the organization of the early blood-clot may occur to aid the primary closure of the large cavity.

To prevent the possibility of tetany the epithelial or parathyroid glands must be avoided in the course of an operation and preserved even if it be necessary to replace accidentally separated ones. These bodies, four in number (two on each side), are known to be occasionally injured by hemorrhages into them at birth, so it is impossible to say whether or not the parathyroid bodies are all present and whether or not the one or two that we may injure are the only ones existing. It is advisable, therefore, to keep in front of the posterior capsule or very close to it in extirpating the diseased portion of the thyroid gland and not to remove any small gland-like structures.

However, those surgeons whose patients have had tetany following operations for goiter have probably removed the lateral lobes of the thyroid and left an isolated bit of the isthmus without blood-supply. Even if the parathyroids were not removed their circulation was destroyed. The cases reported have usually recovered after a tedious convalescence and in spite of much experimentation.

The mortality in simple goiter is but a fraction of 1 per cent., while that of exophthalmic goiter varies from 1 to 2 per cent.

Relapses occasionally follow the removal of adenomas. They are also observed in some cases of Graves' disease due to an insufficient removal of gland or to an increase in what was left which may not show or cause symptoms for some years after the primary extirpation. The indications are to remove more of the gland.

THE RELATIONSHIP OF THE CLINICAL AND PATHOLOGIC ASPECTS OF EXOPHTHALMIC GOITER*

LOUIS BLANCHARD WILSON

Four years ago I published my studies on the pathology of the thyroid glands from 294 cases of exophthalmic goiter,[1] and a little later on the pathology of the thyroids from 600 cases of simple goiter.[2] In the first group of cases I showed that it was possible, from a study of the glands, supplemented only by a knowledge of the age and sex of the patient, to state on broad general lines: first, that the patient had or did not have exophthalmic goiter as we then defined it; second, the stage of the disease at the time the gland had been removed; and, third, approximately the severity of the disease. This I found could be done with a fair degree of accuracy in more than 85 per cent. of the cases studied.

Since that time Plummer,[3] of the Mayo Clinic, from his study of over 1000 exophthalmic and 1200 simple goiter cases which had been operated on, has shown that he is able to predicate, from a study of the clinical aspects of the cases only, first, whether or not the gland was hyperplastic, adenomatous, or with advanced colloid changes; second, with considerable detail the degree of hyperplasia, adenomatosis, or colloid change; and, third, what effect might be expected from removing a given portion of the gland in any individual case. This he has been able to do in above 95 per cent. of the cases studied.

This evidence of the definite and constant relationship of the clinical symptoms and pathologic conditions in cases of exophthal-

---

* Read by title before the Second Tri-State Medical Meeting of Washington, Idaho and Oregon, Portland, Ore., July 5–6, 1912. Reprinted from "Northwestern Medicine," January, 1913, pp. 1–5.

mic goiter was not mere guessing, and was so much in advance of the claims of other observers that, quite naturally, it attracted considerable attention, and several other workers have reported their observations along similar lines. As was to be expected, some of these observers do not agree with the conclusions of Plummer and myself, one of the most recent papers, for example,[4] claiming that "neither specific nor constant anatomic changes in the thyroid of exophthalmic goiter have as yet been demonstrated."[4]

I, therefore, wish to point out some of the reasons for the seeming disagreement between observers in the clinical and pathologic fields concerning exophthalmic goiter, and to explain why we think our own observations should carry weight.

1. The number of cases in our series has been sufficiently large to permit us a broad view of the field, to furnish large groups of cases closely resembling each other, and to permit us to differentiate by comparison the essential from the unessential symptoms and lesions. Every scientist knows that it is impossible to classify correctly any large group of objects from even the most minute knowledge of but a few of its representatives. Up to July 1, 1912, 1355 patients had been operated on in the Mayo Clinic for exophthalmic goiter and 1941 for simple goiter. Ninety per cent. of these cases have been seen personally by Plummer, and the histories of the remaining cases have been carefully reviewed by him. The removed glands from practically all the cases have been studied in the gross and in fresh sections in the laboratory, and those from about one-half of the cases have been studied in detail, both in fresh and especially in fixed-tissue preparations by myself.

2. The clinical and pathologic studies were made absolutely independent of each other until a large group of cases had been collected, when they were then compared case by case. This has insured the keeping of the mind of each observer entirely free from bias by knowledge received from the other. While for the diagnosis and final summary of individual cases there can be no doubt that one should be cognizant of all the facts to be learned, it cannot be too strongly urged that, in the trying out of a new hypothesis, unconscious bias must be excluded by keeping each observer in

ignorance of the facts which have been noted from a different viewpoint. Moreover, the ability accurately to make and correctly to summarize the detailed observations, necessary on both the clinical and pathologic sides of such a study as this, is beyond the skill of any one man. Much of the disparity which has been reported by other observers between the histopathology of the thyroid and the clinical symptoms of exophthalmic goiter is very obviously due either to the attempt on the part of an able clinician to interpret a pathologic picture, the details of which he was incapable of assembling in their proper relationships, or, quite as frequently, on the other hand, to the inability of a good pathologist to appreciate the correct meaning of the various clinical symptoms.

3. Many observers have failed to appreciate that a disease with such a protean symptom-complex as goiter must present a similarly varied pathology. It is necessary not merely that one should see that this case was clinically exophthalmic goiter and that pathologically it presented a hyperplastic thyroid, but it is necessary also to determine with the most minute detail all the varied symptoms of exophthalmic goiter and the stages thereof, and to study with equal minuteness of detail every phase of the pathology. For example, Plummer's history sheet for a case of goiter notes specifically over 150 separate items, while the tabulation of the pathologic data on the removed gland covers over 100 points. Having thus analyzed each case clinically, it has been necessary to formulate a picture which should embody the clinician's estimate of the clinical condition not only which is now present, but also that which has preceded. And it has been equally necessary that the pathologist should not merely take a cursory glance at the gross appearance of the gland and of a few sections cut therefrom, but that he should attempt to estimate, as one might from the study of all the details of a large factory, the size, functioning capacity, and excretory index of the gland. Here let me call attention again to the importance in studying the effect on the general system of the work of the thyroid or of any other secretory gland, of giving heed not only to what is found *in* the gland at any one time, but also to what is continually *going out*

of the gland. Every gland which, like the thyroid, has both an excretory and a storage function must be gaged not only by the contents of its warehouse, but likewise by its manufacturing capacity and by its shipping facilities.

4. The correctness of the conclusions, both clinical and pathologic, to a great extent must be checked up by the subsequent history of a large series of human cases which have been operated on. Complicated functional experiments on laboratory animals, while in themselves extremely important and giving much valuable data, can never possess the accuracy, as related to human beings, of observations on human beings themselves. The animal experimenter sometimes becomes a bit arrogant in his assumption that only experiments on lower animals can be kept free of interfering factors. As a matter of fact, however, any one who is familiar, for example, with the problems of breeding and rearing dogs, with their variations and accidents and diseases, knows that it is more difficult to lay a foundation of "normality" in any respect on the pathologic animals collected from the public pound than to lay such a foundation from a clinical, surgical, and pathologic study of intelligent human beings. Many of the conclusions of scientific observers have been drawn from observations on supposedly normal dogs which any reasonably intelligent kennel man would at once point out as aberrant, if not pathologic, in many of the essential characteristics in question. We are making a great many observations on dogs at Rochester, but we recognize the limitations of the data so obtained.

What now are the essential factors in the hypothesis which has enabled Plummer and myself to show that there is a distinct relation between the clinical and pathologic pictures of exophthalmic goiter? Without going into detail, they may be stated briefly as follows:

1. The thyroid gland is composed almost wholly of secreting tissue.

2. Anything which is made by the gland must get into the circulation before it can affect distant parts.

3. The thyroid gland is also capable of storing up material.

4. Certain symptoms of exophthalmic goiter—symptoms of pressure on the trachea and adjacent vessels and nerves—are due to increase in size of the gland largely from its overfilled storage capacity.

5. Certain other symptoms of exophthalmic goiter—the acute toxic symptoms—seem due primarily to something made in the thyroid gland which passes into the general circulation and acts directly on distant vital organs.

6. Yet other symptoms of exophthalmic goiter are the secondary result of—(*a*) degenerative changes produced in distant organs after their affection by thyroid secretion, and (*b*) of the disturbance of the normal interrelations of these organs themselves.

We must recognize the fact that the thyroid gland must not only vary greatly in its function at different periods of the life of the individual, but also that it does vary greatly in the relative development of its gland units even in individuals whose histories are free from clinical manifestations ascribable to changes in the gland. From the embryologic standpoint, we formerly supposed that the thyroid in man was derived, as in the lower vertebrate animals, from three buds—a median and two lateral. Recent studies,* however, have shown that the thyroid in man is derived entirely from a single bud which appears as an evagination of the epithelium of the pharynx, beginning in the center of the ridge between the first and second ventral pharyngeal grooves. This, the middle thyroid anlage, becomes bilobed at its distal extremity while still in tubular connection with the pharynx. The lumen becomes closed just before the dissociation of the anlage from the pharynx, and the anlage then becomes a broad crescentic band of tissue stretched transversely ventral to the pharynx and gradually becoming displaced caudally. In embryos of about 50 mm. in length there are developed, in the center of each of the lateral lobes

---

* Grosser says, "Up to the present no evidence has been advanced in favor of the widely accepted view that the (ultimo-branchial) bodies become converted into thyroid tissue and such a transformation is rendered highly improbable by the results of comparative investigation. The name lateral thyroid anlagen, which has been applied to the ultimo-branchial bodies, is therefore to be rejected." (Keibal and Mall: "Manual of Human Embryology," 1912, vol. ii, pp. 469–472.)

of the thyroid, areas showing increased growth and a closer grouping of the cords. These cell-cords now develop more or less well-defined lumina and then segment into separate groups of cells (follicles), some of which continues to possess lumina, while others are lumenless. There is no evidence that in man the thyroid functionates at any time while the thyroglossal duct is still patulous except in anomalous conditions. Phylogenetically, however, the thyroid is undoubtedly an organ whose secretion in certain lower animals finds its way directly into the alimentary canal.

It will thus be seen that the thyroid gland is really a congeries of a great number of groups of cells which may be found even in the adult in any stage of development from masses of unarranged embryonic cells (Wölfler's rests) through tightly packed, centrically arranged groups of embryonic epithelial cells, to well-developed follicles lined with epithelium, evidently capable of secreting into the well-marked central cavity. With such a great variety in the stages of development of the epithelium of the gland existing even in the adult, in whom there are no symptoms of goiter change, the pathologic changes produced may present an enormous variety, of which the following are the more important:

1. The simplest change which we find appearing upon the normal (resting thyroid) is *hyperemia*. This is quickly brought about by excitement (sexual, fear, etc.) and is usually very fleeting. Yet we must remember that hyperemia always materially increases the index both of secretion and of excretion of the gland.

2. Associated with hyperemia may be *hemorrhage*, which may be so extensive as to cause sudden and great enlargement of the gland tissue and frequently results in secondary cyst formation.

3. *Acute inflammation* of the thyroid may occur as the result of traumatism or as an incident in the course of a general bacterial disease.

4. The most important pathologic changes in the thyroid gland, however, as related to goiter, are those concerning the parenchyma. The simplest of these is *hypertrophy*, which invariably follows hyperemia and that very quickly. The functionating cells of the parenchyma become swollen and columnar with nuclei

approaching their free extremities; the acini become dilated and the secretion acquires a relatively lowered density, thus more readily passing into the circulation. Simple hypertrophy of the thyroid may result temporarily in secretion and excretion beyond physiologic limits.

5. *Progressive hyperplasia* of the thyroid consists of an increase in the number of parenchyma cells—which are also almost invariably hypertrophic—either in the original single or in multiple new layers. Accompanying this is an overgrowth or stretching of the stroma or an infolding of the acinar walls with papillomatous growths into their cavities, providing basal attachment for the increased number of cells. The secretion in early hyperplasia has always a low density, which, however, rises as the increased function is prolonged. Many thyroids in cases of exophthalmic goiter show every portion of the gland in an active hyperplastic condition, all evidence of embryonic acini having disappeared, and Wölfler's rests entirely absent or perceptibly crowded into lesser space by the pressure of the swollen epithelium of the acini. This condition is *par excellence* that associated with progressive toxic symptoms of exophthalmic goiter. Clinically, both lobes of the glands are affected and the enlargement is described as bilaterally symmetric, though the right lobe is usually larger than the left.

6. *Adenomatosis* of the thyroid consists of a diffuse multiplication of the embryonic acini or the development of new acini from Wölfler's rests. Such a diffuse increase in the number of acini should be sharply differentiated from the formation of adenomas. Adenomatosis may be associated with hypertrophy or hyperplasia of the contained parenchyma and thus be the condition present in the thyroids in cases which develop toxic symptoms late in the course of simple goiter. Sometimes, however, the parenchyma cells in the newly formed acini remain cuboid and without hyperplasia.

7. True *adenomas* of the thyroid can be identified only when they are encapsulated. Histologically, they are of two types: (*a*) Fetal adenomas, in which the parenchyma is of true fetal type, *i.e.*, consisting either of cordons, embryonic tubules, or more

or less lumenless groups of spheroid cells or of combinations of these group units. (*b*) Adult adenomas, which are encapsulated tumors in which the parenchyma has taken on adult characteristics, that is, it consists largely of spheroid follicles containing lumina lined with cells of adult type. The tissue of adult adenomas may take on all the changes which have been noted in the thyroid gland tissue outside the encapsulated tumors. While it may be true that adult adenomas develop from fetal rests, there is insufficient evidence to demonstrate this beyond peradventure and, for both pathologic and clinical purposes, it is best sharply to differentiate the two on the lines indicated above.

8. Of the *retrogressive* changes in the thyroid, *retention of secretion* is the most common and approaches nearest to the normal physiologic state. There can be no doubt but that the thyroid gland is not only an actively secreting organ, but that it has, normally, a storage function as well. It is impossible, however, to say what constitutes normal storage function. When, however, the retention of secretion has reached the stage at which by pressure, by enfeebled circulation, or by both, the material contained in the glandular acini is so dense that the index of absorption is obviously decreased and, when the parenchyma cells lining the follicles are flattened out and apparently no longer secreting, there can be no doubt that we have a pathologic condition. This extreme retention of secretion is the essential element in the formation of the so-called colloid or simple goiters. Some areas in such thyroids occasionally contain sufficiently active parenchyma that it may take on hyperemia or hyperplasia and permit of even the somewhat rapid absorption of long quiescent colloid. Such a condition explains why we occasionally have, arising late in the history of old colloid goiters, a condition of acute though usually mild thyrotoxicosis.

9. *Atrophy* of the parenchyma of the thyroid results, as elsewhere in the body, from overwork, pressure, and lack of nutrition. The cells, becoming flattened from pressure of retained colloid secretion, may die and desquamate from the acinar walls. This condition must be differentiated, however, from a rapid desqua-

mation and disintegration of the parenchyma cells which occasionally occurs in the course of acute hyperplasia. We have found this latter condition in a few cases which have been rapidly fatal. It appears to be exactly what one would expect in the case of an intense locally acting toxin.

10. Of the *terminal degenerations*, aside from *colloid*, which is often overlooked, in both the parenchyma and stroma, *hyaline*, *amyloid*, and *calcareous* changes are not uncommon. These, however, appear to have no clinical significance other than that their presence indicates terminal stages of an old process.

We may therefore classify the histologic conditions met with in the thyroid glands as follows:

- I. Embryonic (undeveloped) thyroid.
- II. Normal (resting) thyroid.
- III. Vascular changes.
    - 1. Hyperemia.
    - 2. Hemorrhage (including resulting cyst formation).
- IV. Inflammations.
- V. Progressive changes.
    - 1. Hypertrophy (functional, with hyperemia).
    - 2. Hyperplasia ("exophthalmic" goiter).
    - 3. Adenomatosis (multiplication of acini without encapsulation).
    - 4. Regeneration of previously atrophied parenchyma.
- VI. Retrogressive changes.
    - 1. Retention of secretion (colloid goiter).
    - 2. Atrophy (of parenchyma).
    - 3. Degenerations.
        - (*a*) Colloid (of parenchyma and stroma).
        - (*b*) Hyaline.
        - (*c*) Amyloid.
        - (*d*) Calcareous.
        - (*e*) Cystic.
- VII. Tumors.
    - 1. Benign.
        - (*a*) Fetal adenomas (encapsulated).
        - (*b*) Adult adenomas (encapsulated).
    - 2. Malignant.
        - (*a*) Mesotheliomas.
        - (*b*) Carcinomas.
        - (*c*) Sarcomas.

The relationships of the above pathologic classification to clinical conditions in certain respects may be indicated more clearly by the following broad general statements:

1. The thyroid gland removed from a young patient in the early months of acute thyrotoxicosis (exophthalmic goiter) shows hypertrophy and hyperplasia of the parenchyma, with a small

amount of a thin and but slightly stainable secretion within the acini. The size of the gland and the distribution and degree of hyperplasia are proportionate to the intensity of the symptoms.

2. The thyroid gland from a young patient who has had acute thyrotoxicosis four months to a year shows a much more active hyperplasia and a much larger amount of stainable secretion in the acini throughout the gland. This pathologic picture corresponds to a period of great intensity of the toxic symptoms which Plummer[5] has pointed out usually occurs in the latter half of the first year of acute Graves' disease.

3. The thyroid gland in a young patient who has had acute Graves' disease for a year or more usually shows at least three phases of pathologic change scattered irregularly throughout the gland as follows: (*a*) An active parenchymatous hyperplasia, like that described in No. 1; (*b*) a reduced parenchymatous hyperplasia with a dense stainable secretion in the acini, like that described in No. 2; and (*c*) areas in which the parenchyma cells are atrophied or desquamated from the walls of the acini, which are distended with intensely staining colloid.

4. The older the patient at the time of onset of acute thyrotoxicosis, the more quickly do colloid changes appear in the thyroid.

5. The thyroid from a patient who has somewhat rapidly developed a typical picture of exophthalmic goiter with exophthalmos after years of simple goiter presents a picture of advanced colloid change throughout most of the gland, but usually with *thinned* rather than with desquamated parenchyma and with scattered areas of somewhat actively functionating parenchyma which may be markedly hyperplastic. It is sometimes impossible to distinguish this pathologic condition from that described in No. 3.

6. The thyroid gland from a patient who has had symptoms of thyrotoxicosis very slowly developing throughout a period of years with a predominance of cardiac symptoms and with little if any exophthalmos is usually found to present a histologic picture of—(*a*) diffuse adenomatosis or (*b*), more usually, of encapsulated multiple adenomas, almost invariably of the fetal type, or (*c*) regenerations of previously atrophied parenchyma. These cases,

however, as pointed out by Plummer,[5] are not true exophthalmic goiter.

While the above general statements indicate broadly the lines of relationship which are usually found existing between the pathologic and clinical conditions, I must urge the futility of attempting to coördinate the clinical and pathologic findings on any given case without making of it a special problem to be studied in minute detail both by a skilled clinician and by an experienced pathologist.

REFERENCES

1. Wilson: "Amer. Jour. Med. Sci.," 1908, vol. cxxxvi, pp. 851-861.
2. Wilson: "Sur., Gyn., and Obst.," October, 1909, vol. viii, pp. 588-605.
3. Plummer: "Relation of the Symptomatology and Pathology to Operative Mortality in Exophthalmic Goiter," read before the Section on Practice of the American Medical Association at Los Angeles, June 29, 1911.
4. Marine: "The Anatomic and Physiologic Effect of Iodin on the Thyroid Gland of Exophthalmic Goiter," read before the sections on the Practice of Medicine and Surgery of the American Medical Association, Atlantic City, June, 1912.
5. Plummer: Article (with C. H. Mayo) in supplementary volume of Keen's "System of Surgery," vol. vi, pp. 333-337.

PATHOLOGIC ANATOMY OF GOITER*

(A MACROSCOPIC AND MICROSCOPIC STUDY OF FRESH MATERIAL FROM 2500 CASES)

WILLIAM CARPENTER MACCARTY

Speculation in science often leads to self-deception and has caused many excellent and conscientious observers to write fiction regarding scientific subjects. Such statements as the following are found in literature written by some of the best observers upon the subject of goiter: "In a majority of the cases of exophthalmic goiter occurring in non-goiterous regions, and, to a much less extent, in those occurring in goiterous districts, the hyperplasia develops from a normal gland base." Such a statement is not based upon proved facts, but upon observations which have been unconsciously colored by speculation. No one can say positively that an exophthalmic goiter "develops from a normal gland base," because no one has ever seen an exophthalmic goiter in the process of development. Other statements occur, such as: "Tracing the development of hypertrophy and hyperplasia from the normal gland, the first change noticed is the increased blood supply." This statement may be true, but it, too, is based upon speculation and not upon actual observation of a developing gland. Actual facts should not be mixed with unlabeled speculation.

An endeavor, therefore, to separate the known from the unknown, regarding the pathology of goiter, leads the writer to an extremely academic consideration of the subject, based upon examinations of over 2500 fresh specimens which were removed at operation in the Mayo Clinic. These specimens were examined macroscopically and microscopically immediately after their removal. They were, therefore, studied in a perfectly fresh condition without the artefacts coincident to fixation. It was noted that the specimens divide themselves into two groups, namely: a group composed of symmetric thyroids and a group of asymmetric or nodular thyroids.

---

* Read at the annual meeting of the Medical Society of the State of New York, at Albany, April 18, 1912. Reprinted from "New York State Journal of Medicine," October, 1912, pp. 595–599.

The symmetric thyroids vary in size from that of a normal fetal thyroid to many times the normal. Upon gross examination of the cut surface of the symmetric specimens two very definite pictures are noted, namely, meaty glands with acini which are not distended and hence not readily visible (Fig. 182, F), and glands consisting of large acini, which are filled with jelly-like colloid material (Fig. 182, D). These are, however, descriptions of the extreme conditions, because many specimens though meaty also contain some colloid material (Fig. 182, E). The amount of colloid material found varies within rather wide limits.

The two conditions just described bear no apparent relation to the size of the specimen.

Microscopic examination of these glands reveals varying pictures of the acini, or gland units. The extremes of these are small acini with epithelial hyperplasia without colloid (Fig. 182, F) and large acini with colloid and no epithelial hyperplasia (Fig. 182, D). Both epithelial hyperplasia and intra-acinar colloid are, however, often present in the same gland (Fig. 182, E). The size of the acini varies in all of these glands and even in the same gland, but the variation is not sufficiently great to destroy the shape of the thyroid. The specimens are diagrammatically represented in the accompanying figures.

Fig. 182 contains all the normal shaped thyroids. The first of these is the fetal thyroid (A), the glandular unit, or acinus, of which is a group of cells without a patent lumen (a).

The "normal adult thyroid" (B) is composed of acini (b), which consist of low or flat cuboid cells, with a small amount of protoplasm, surrounding a lumen, which is filled with a colloid substance. One also occasionally finds an adult thyroid (C) which contains, in addition to the colloid acini (b), many acini of the fetal type (a).

Where the "normal" thyroid ceases to be normal and begins to be pathologic is still undetermined. At autopsy many adult thyroids, in non-goiterous individuals, show evidence of abnormal changes, such as the presence of dense connective-tissue and lymphocytic infiltration.

There is, however, not infrequently seen a thyroid (D) which is larger than the normal thyroid, and consists of acini (d) similar to those found in the normal thyroid with the exception that they are larger and contain more colloid.

Other specimens (E) consist of acini which are lined with large cuboid cells and which contain colloid material (e). The walls of these are often crenated to form intra-acinar papillary projections (e). Acini of all of the above described types are found also in such a specimen.

The last type (F) of symmetric specimens consists of acini (f) which contain little or no colloid material, but the lumen of these is almost completely filled with the large hypertrophic or hyperplastic cells.

Many gradations occur between these types so that it is often difficult to determine that a gland belongs to any one pure type. These are the main and only distinguishing characteristics which are seen in the thyroid.

The sequence of development of these, the anatomic and histologic conditions or stages,—if they are really stages of one condition,—remains undemonstrated in the human thyroid. Marine has stated that the amount of colloid material increases as the hyperplasia decreases. This he has demonstrated experimentally on dogs and fish, but the work has not been confirmed on human material. His work adds experimental evidence to the chemic parallel which exists between the amount of colloid and the amount of iodin, a fact which was pointed out by Oswald.

The essential and dominating features of the specimens, which have passed through the writer's hands, have thus been briefly described without recourse to the terminology, which one finds so profusely distributed in the literature, and which is largely a mixture of clinical symptoms or signs, authors' names, and a certain amount of anatomic description.

It is the writer's belief that knowledge of the thyroid is not sufficient to enable us to recognize all the clinical pictures which may be associated with its pathology, and he has, therefore, refrained from making a pathologic diagnosis in his daily routine reports to the clinician.

The writer has recently described all his specimens without reference to clinical pictures, and the following descriptive, instead of diagnostic, terminology has gradually evolved itself:

The fetal thyroid (Fig. 182, A), which is not seen surgically; the "normal" adult thyroid, which contains some colloid (Fig. 182, B), but which is also not seen surgically; the adult thyroid containing colloid and fetal thyroid (Fig. 182, C), a condition which is seen at autopsy and occasionally at operation in patients who are explored for a possible thyroid hyperplasia; the hypertrophic thyroid with large colloid acini (Fig. 182, D), a condition which is seen in cases with suggestive clinical symptoms of hyperthyroidism similar to those found in the next group, which may be described as the hypertrophic thyroids with epithelial hypertrophy or hyperplasia without intra-acinar colloid (Fig. 182, E), a condition which is definitely associated with a certain symptom-complex which we call hyperthyroidism. This clinical condition is also often associated with a hypertrophic thyroid with epithelial hypertrophy and colloid (Fig. 182, E). These include all of the symmetric or thyroid shaped thyroids, which are found normally and pathologically.

Since descriptions, rather than diagnoses of the pathology found at operation, have been sent to the clinician, the latter has shown more accuracy in correlating his findings with other conditions than the pathologic and clinical extremes.

All the pathologic conditions of the gland which come under the heading of goiter do not allow the gland to retain its original shape. Asymmetric or nodular glands contain usually, if not always, one or more encapsulated oval or round adenomas (Fig.

183). These vary greatly in size and number. They may be millimeters or centimeters in diameter; they may be single or there may be so many present that the gland becomes a nodular mass (Fig. 183, B).

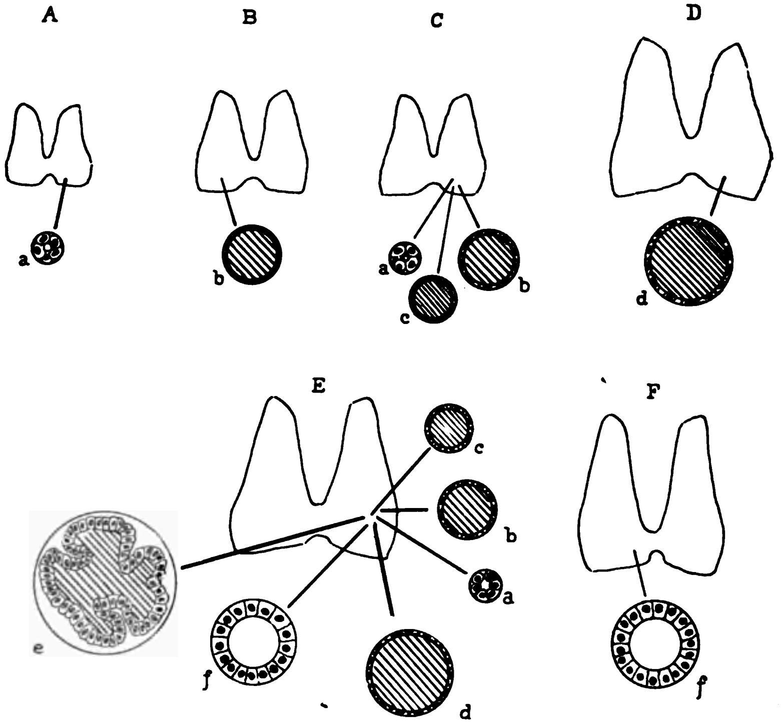


Fig. 182.—Diagrams of symmetric normal and pathologic (goiterous) thyroids: A, Fetal thyroid with a fetal glandular unit (a). B, Adult thyroid and adult unit (b). C, Adult thyroid with adult and fetal units (a, b, c). D, Hypertrophic thyroid showing a dilated acinus or unit filled with colloid (d). E, Hypertrophic thyroid with some areas of fetal, normal, dilated, hypertrophic parenchymatous units (a, b, c, d, e, f). F, Hypertrophic thyroid (meaty) with hypertrophic parenchymatous units (f).

The capsule of the adenoma is fibrous connective tissue, which varies greatly in thickness and density. It is frequently calcareous. The body of the tumor upon gross section is variable. The cut surface of the simplest undegenerated tumor is firm, uniform, and free from macroscopically visible colloid. The acini of such a tumor are fetal in type (Fig. 182, a; Fig. 183, a), although they may contain a very small lumen (Fig. 183, c). The acini are more widely separated by a delicate interacinar stroma than in the fetal thyroid. Upon the cut surface one readily recognizes that one does not always find the simple adenomas which have just been described; colloid material is frequently seen in large amounts (Fig. 183, B, b and d); such acini are easily grossly visible. Upon microscopic examination the acini are found to be large, lined with flat cuboid cells, and filled with colloid (Fig. 183, B). The colloid acini are indistinguishable from those found in colloid thyroids (Fig. 182, D) described above. If one searches such a tumor, fetal acini are certainly to be found. Acini composed of hypertrophic cells are occasionally found (Fig. 183, B).

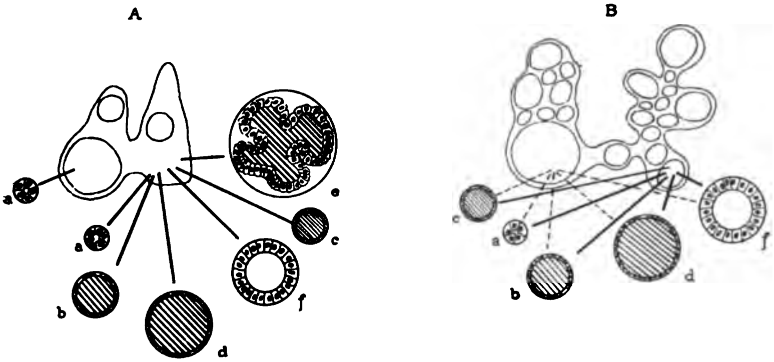


Fig. 183.—Diagrams of asymmetric pathologic (goiterous) thyroids: (A) A thyroid containing a simple adenoma with its fetal unit (a) and the surrounding gland with the various units, which are often found (a, b, c, d, e, f). (B) A greatly distorted thyroid containing many adenomas and the units, which one often finds in them associated with the simple adenoma units (a).

Red, brown, or old yellowish hemorrhagic areas are often found in these tumors. Areas of dense and even calcareous tissue are also frequent. Many tumors are found in which a part or all of the tissue within the capsules has become liquefied. The contents of such a degenerative cyst have an amber color or are hemorrhagic. They practically always contain cholesterin crystals.

The surrounding gland in which these tumors are present, presents the same acinar characteristics which have been described above for the symmetric thyroids. In the majority of specimens the surrounding gland is composed of the colloid and fetal acini

(Fig. 183, A). The acini do, however, sometimes present a picture of pressure atrophy, which is not seen usually in the uncomplicated symmetric thyroid. One may describe adenomas of the thyroid according to the following descriptive key:

Degenerating Degenerated Calcareous Hemorrhagic Cystic	Single or multiple	Simple Colloid hypertrophic Hypertrophic parenchymatous	Thyroid adenomas (In a or an)	Adult Adult and fetal Colloid hypertrophic Hypertrophic or hyperplastic parenchymatous Colloid hypertrophic or hyperplastic parenchymatous	Thyroid

These anatomicopathologic observations may be studied in the light of chemic and experimental work.

The main features connected with the experimental findings relative to the thyroid may be briefly stated to have begun with Reverdin's (1882) observation regarding the severe disturbances which he found to occur in man after total extirpation of the thyroid. This observation was followed by Schiff's efforts (1894) to transplant thyroid tissues after thyroidectomy. The results were not completely satisfactory, although they gave sufficient encouragement for further investigation. Bircher (1890) tried the effect of transplanting thyroid tissue into a myxedematous patient. His efforts were followed by good but not perfect results. Horsley (1890) transplanted the thyroids of monkeys and sheep without striking results. The imperfect results of these experiments were considered to be probably due to the method of transplantation. von Eiselsberg, therefore, acting upon this supposition, transplanted the thyroid into the abdominal wall of thyroidectomized animals. His work led him to say that further work would be necessary before definite conclusions could be made. Payr (1906) transplanted the thyroid into the spleen in thyroidectomized animals without great practical results. Other experimenters have repeated these experiments with results which merely demonstrate the essential nature of the organ to animal economy and the relative value of transplantation to therapy.

The relation of the parathyroids to these experiments will not be considered at this time.

Knowledge of the chemic nature and the supposed active principles of the thyroid extends back to a period of several years before animal experimentation upon the thyroid came into use. The iodin content of the thyroid was known to Oidtmann (1858), and the water-supply of regions of endemic goiter and cretinism were studied by Chatin (1859). The work of Baumann (1896), however, demonstrated that iodin was a normal constituent of the thyroid and was present in larger proportions than in other organs of the body. From his work detailed studies have developed upon this constant constituent with the discovery of its incorporation with protein cellular constituents. The iodized proteid was given the name iodothyrin or iodothyroglobulin. The essential nature of the gland and the chemic findings gave rise to speculation, which led to various theories, namely, the "secretion theory" (Baumann, Roos, Oswald, and others), the "neutralization theory" (Notkin and Blum), and the "biologic reversion theory" (MacCarty).

The experimental work which has been done on the thyroid, especially the work on extirpation and transplantation, has apparently demonstrated the essential nature of the organ to economy. It has led to the use of thyroid extract, with effective results, in cases of apparent thyroid insufficiency. It has led the surgeon to more accurate surgical procedure and has enabled him to cure many patients and relieve many others.

The gross and microscopic pathology teaches us that the condition which we call goiter—at least in its more advanced condition—is something more than a localized condition. The thyroid itself is but a part of a pathologic complex, which makes up a clinically complex picture, especially in cases of hyperthyroidism. In spite of the excellent chemic, surgical, clinical, and pathologic research, which has given us a much clearer idea of goiter, very little is known about the etiology or indeed the physiology of the gland itself.

New paths of research should be utilized in conjunction with the research, which has already been done.

Not until gastric juice had been obtained by means of a fistula were we able to obtain the slightest conception of gastric secretion. Not until then were we able to study the properties of gastric juice and the actions of stimuli upon its production. Not until we were able to collect saliva from the salivary ducts were we able to study the chemic and physical properties of its active principle and to control its production by stimulation.

These facts are so clear and our knowledge so empirical and so limited that they make us fear that the truth about the thyroid is far distant.

The field, however, should not be a discouraging one. Indeed, it is filled with the greatest and broadest interest and possibilities because it involves something more than experimental surgery and chemistry; it involves, first of all, the discovery experimentally of an animal with a patent thyroid duct from which secretion may be obtained. This is the work of a zoölogist or zoölogic physiologist, and his attention should be drawn to its broad experimental interest and practical significance.

Somewhere in the animal kingdom there is probably a thyroid which functionates normally with a patent duct or analogous organ. Whether this animal is aquatic, terrestrial or both is, so far as the writer knows, still undetermined.

This brief academic review is but a confession of our limited scientific knowledge of the thyroid and its pathologic condition which we know as goiter.

Goiter is not a simple condition. Its pathology demands something more than text-book diagnoses of "exophthalmic" and "colloid" goiters to be handled by simple types of treatment be they medical or surgical.

REFERENCES

1. Marine. "Arch. Int. Med.," September, 1911.
2. Oswald: "Virchow's Arch., 169 (1902); Habilitationsschrift (1900), Strassburg.
3. Reverdin: Quoted from Tigerstedt's "Lehrbuch der Physiologie des Menschen," vol. i.
4. Schiff: "Rev. Méd. de la Suisse romande," 1894, Nos. 2 and 8. "Arch. exp. Path.," vol. xviii.
5. Bircher: "Volkmann's Sammlung klin. Vorträge," 1890, No. 357.
6. Horsley: Festschrift Virchow," vol. i, Berlin, 1891, and British Med. Jour., vol. i, p. 287 (1890).

7. von Eiselsberg: "Wien. klin. Woch.," 1892, Nos. 5 and 6.
8. Payr: "Arch. klin., Chir.," 1906, vol. lxxx, Nos. 3 and 4.
9. Oidtmann: "Preisschr.," Würzburg, 1858.
10. Chatin: Quoted from von Eiselsberg, "Deutsche Chir.," 1901.
11. Baumann: "Zeit. phys. Chem.," 1896, vol. xxi, p. 319.
12. Roos: "Zeit. phys. Chem.," 1896, vol. xxii, p. 16.
13. Notkin: "Wien. med. Woch.," 1895, No. 45; "Virch. Arch.," 1896, p. 144, Suppl. 224.
14. Blum: "Berlin. klin. Woch.," 1898, No. 43.
15. MacCarty: "Amer. Jour. Med. Sci.," June, 1909.

GOITER AND ITS RELATION TO ITS STRUCTURAL AND PHYSIOLOGIC UNITS*

WILLIAM CARPENTER MACCARTY

The evolution of our knowledge of the subject of goiter may be briefly stated to have begun with the recognition of four clinical facts, *i. e.*, the presence of a tumor of the thyroid gland; the presence of a condition called myxedema, which was found in association with changes in the gland; a condition known as cretinism, which was associated with thyroid changes; and a clinical complex in association with protrusion of the eyes and enlargement of the gland. Clinicians, surgeons, chemists, hygienists, pathologists, physiologists, embryologists, and zoölogists have endeavored, disconnectedly, to understand the conditions and their etiology.

Experimental surgical experience may be briefly summarized from the beginning of the unsatisfactory efforts of Schiff (1884) at transplantation of thyroid tissue after thyroidectomy. Bircher (1890) tried the effect of transplanting thyroid tissue into a myxedematous patient. His efforts were followed by good but not perfect results. Horsley (1890) transplanted the thyroids of monkeys and sheep without striking results. The imperfect results of these experiments were considered to be due probably to the method of transplantation. Von Eiselsberg, therefore, acting upon this supposition, transplanted the thyroid into the abdominal wall of thyroidectomized animals. His work led him to say that further work would be necessary before definite conclusions could be made. Payr (1906) transplanted the thyroid into the spleen in thyroidectomized animals without great practical results. Other experimenters have repeated these experiments with results which merely demonstrate the essential nature of the organ to animal economy and the relative value of transplantation to therapy.

---

* Read before the Chicago Medical Society October 31, 1912. Reprinted from "Surgery, Gynecology, and Obstetrics," April, 1913.

Partial thyroidectomy in goiter in the hands of Kocher, Mayo, Halstead, Crile, and others has given sufficient empirical satisfaction in the human being to demonstrate its necessity in the treatment of the clinical conditions, which have not responded to any known hygienic, medical, or serum treatment.

A knowledge of the chemic nature and the supposed active principles of the thyroid extends back to a period several years before animal experimentation upon the thyroid came into use. The iodin content of the thyroid was known to Oidtmann (1858), and the water-supply of regions of endemic goiter and cretinism were studied by Chatin (1859). The work of Baumann (1896), however, demonstrated that iodin was a normal constituent of the thyroid and was present in larger proportions than in other organs of the body. From his work detailed studies have developed upon this constant constituent, with the discovery of its incorporation with protein cellular constituents. The iodized proteid was given the name "iodothyrin" or "iodothyroglobulin." The essential nature of the gland and the chemic findings gave rise to speculation, which led to various theories, namely, the "secretion theory" (Baumann, Roos, Oswald, and others), the "neutralization theory" (Notkin and Blum), and the "biologic reversion theory" (MacCarty).

The whole experimental work which has been done upon the thyroid, especially the work upon extirpation and transplantation, has apparently demonstrated the essential nature of the organ to economy. It has led to the use of thyroid extract with effective results in cases of apparent thyroid insufficiency. It has led the surgeon to more accurate surgical procedure, and has enabled him to empirically cure many patients and relieve many others. Hygienists and clinicians have advised change of drinking water and environment, meat-free diet, rest, iodin, belladonna, and special sera, with the result that no recognized specific is apparently known, at least not practised.

The pathologist has been willing to classify the conditions into types by means of a terminology, which is indefinite, semi-clinical, undescriptive, and extremely varied. Zoölogists, embryologists, and physiologists have not had the economic importance of the condition impressed upon them sufficiently to make them devote large amounts of energy and time to the evolution of the organ and its normal function.

After an extensive review of the literature upon the subject and in the presence of accepted facts, namely, that the function of the thyroid is unknown; the etiology of pathologic conditions in and associated with the thyroid is unknown; that therapeusis of goiter, as practised, is empirical; that clinical pictures and pathologic terminology are confusing, and that the condition is of economic importance, the most important question which arises is, in the writer's opinion, simply, What are the actual anatomicopathologic conditions which are found in the thyroid gland?

This question may seem superfluous, indeed academic, in the presence of the extensive descriptions in journals and text-books. The writer's experience, however, with over 3000 fresh specimens which were removed at operation, prompts a confession of inability to group his material into and according to the published classifications and terminology, which have been thus far presented.

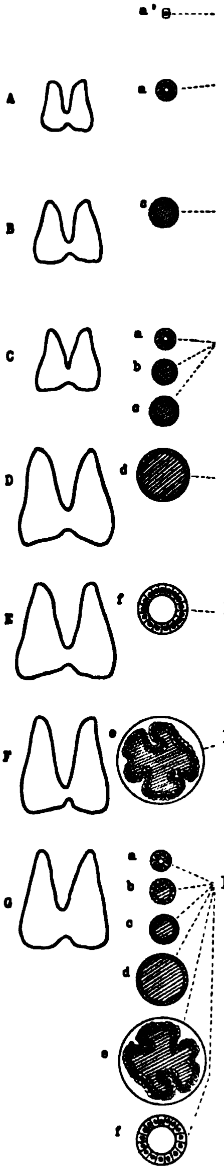
Pathologic diagnoses, which are dictated by clinical diagnoses, are extremely easily made. Diagnoses such as "colloid goiter," "exophthalmic goiter," and "fetal adenoma" are very simple, but they are much simpler than the conditions which are actually present. If, however, progress is to be made in scientific medicine, independent observations must be made by the pathologist, who is uninfluenced by clinical dictation. It is his duty as a scientist, in conditions as chaotic as the subject of goiter, to record what he sees and not to make diagnoses. Correlation may be made after sufficient embryologic, anatomic, zoölogic, clinical, chemic, and therapeutic data are obtained. With this independent attitude toward pathologic conditions it has been found that the material, which has been removed in St. Mary's Hospital, has presented the following facts:

The specimens themselves, as they came immediately from the patient, formed two large groups, namely: the symmetric or thyroid shaped group (Fig. 184) and the asymmetric or nodular group (Fig. 185). Such grouping has absolutely no apparent direct relation to the activity of the gland. It is merely the result of the structural arrangement of the glandular units and their supporting structures. Analysis in the mechanic sense results in the realization that any gland is a system, which is composed of units.

The fetal thyroid is symmetric or thyroid shape, and is composed of histologic units, formed by groups of four to six epithelial cells, which are arranged to form an acinus. An acinar lumen is rarely seen in the fetal thyroid. This type of acinus constitutes, physiologically and histologically, the differentiated thyroid, and differs from the normal adult thyroid only in size and the absence of an acinar lumen.

The postnatal thyroid is symmetric, and is composed of acini or glandular units, which have lumina surrounded by low cuboid cells. The lumina are filled with a so-called "colloid" substance. All acini of such a thyroid are not of the same size although the variation is within small limits. One not infrequently finds a thyroid which has the microscopic appearance of an adult normal thyroid (B). The acini, however, vary in histologic characteristics from that of the fetal thyroid (A), to and including the acini of the normal adult thyroid (B). The thyroid may be described as a postnatal "normal" and fetal thyroid (C).

The three conditions (fetal thyroid, normal thyroid, and postnatal normal and fetal thyroid) just described may be considered "normal" in the light of our present knowledge, although the fact that all the surrounding glandular tissue of adenomas resembles the condition which is seen in the postnatal "normal and fetal thyroid" may serve as a guide to prove the origin of ade-



Descriptive diagnosis: *Undifferentiated fetal adenoma*. Histologic unit.

Descriptive diagnosis: *Fetal thyroid*. Shape: Symmetric or thyroid shape. Histologic unit.

Descriptive diagnosis: *"Normal" thyroid*. Shape: Symmetric or thyroid shape. Histologic unit.

Descriptive diagnosis: *"Normal" and fetal thyroid*. Shape: Symmetric or thyroid shape. Histologic units.

Descriptive diagnosis: *Hypertrophic colloid thyroid or goiter*. Shape: Symmetric or thyroid shape. Histologic unit.

Descriptive diagnosis: *Hypertrophic parenchymatous thyroid or goiter*. Shape: Symmetric or thyroid shape. Histologic unit.

Descriptive diagnosis: *Hypertrophic colloid and parenchymatous thyroid or goiter*. Shape: Symmetric or thyroid shape. Histologic unit.

Descriptive diagnosis: *Hypertrophic fetal, colloid, and parenchymatous thyroid or goiter*. Shape: Symmetric or thyroid shape. Histologic units.

Fig. 184.—Symmetric or thyroid-shaped thyroids or goiters.

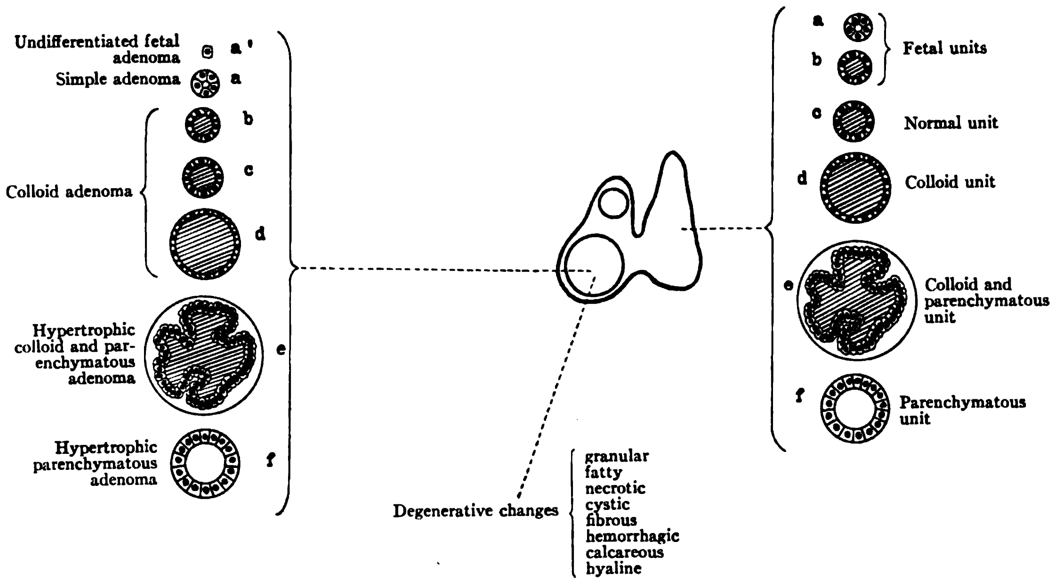


Fig. 185.—Asymmetric or nodular thyroids or goiters.

nomas in embryonic irregularities in differentiation or reaction to normal stimuli.

The symmetrically hypertrophic thyroid, which is seen by the surgeon as goiter, presents definite macroscopic and microscopic pictures, which may be grouped under four headings. This grouping may be done purely upon a histologic basis.

The simplest hypertrophic thyroid, *hypertrophic colloid thyroid* (D), consists of acini, which are larger than one finds in the "normal" thyroid. They are readily visible grossly and contain glistening colloid. The condition is apparently a diffuse or general reaction to some stimulus. Such thyroids have been removed in cases with a symptom-complex which has been clinically taken to be mild "hyperthyroidism." In most of such cases some small amount of hypertrophic and hyperplastic cells are often found. This gland corresponds to the condition which Marine has called the cured gland, the condition which occurs experimentally after the administration of iodin. Whether such a specimen has passed through the histologic picture of marked epithelial hyperplasia is impossible to determine with our present material and method. It leads up to and is not definitely marked off from the third hypertrophic gland in the diagram, *i. e.*, *hypertrophic colloid and parenchymatous thyroid* (F).

Before considering this combination gland, however, the *hypertrophic parenchymatous gland* (E) should be described. Grossly, it is a meaty symmetric thyroid. Histologically, one deals with an acinus which varies in size but which is usually small,—more often about the size of the normal acinus,—but which is composed of hypertrophic or hyperplastic cells, which surround a lumen which is usually not filled with "colloid" material. The fourth hypertrophic symmetric thyroid is composed of acini (*a*, *b*, *c*, *d*, *e*, *f*) which are represented in all the foregoing thyroids. Such a specimen may be descriptively called a *hypertrophic, fetal, colloid, parenchymatous thyroid* (G).

All the pathologic conditions of the gland which come under the heading of goiter do not allow the gland to retain its original shape. Asymmetric or nodular glands, which comprise the second group (Fig. 185), contain usually; if not always, one or more encapsulated oval or round adenomas. These vary greatly in size and number. They may be millimeters or centimeters in diameter; they may be single or there may be so many present that the gland becomes a nodular mass.

The capsule of adenomas is fibrous connective tissue, which varies greatly in thickness and density. It is frequently calcareous. The body of the tumor upon gross section is variable. The cut surface of the simplest undegenerated tumor is firm, uniform, and free from macroscopically visible colloid. The acini of such a tumor are fetal in type (Fig. 184, a; Fig. 185, a), although they may contain a very small lumen (Fig. 185, b). The acini are more widely separated by a delicate interacinar stroma than in the fetal thyroid. Upon the cut surface one readily recognizes that one does not always find the simple adenomas, which have just been described; colloid material is frequently seen in large amounts; The colloid-containing acini are easily grossly visible. Upon microscopic examination the acini are found to be large, lined with flat cuboid cells, and filled with colloid (Fig. 185, c, d). The colloid acini are indistinguishable from those found in symmetric thyroids, described above. If one searches such a tumor, fetal acini are certain to be found. Acini composed of hypertrophic cells are occasionally found (Fig. 185, e, f).

Red, brown, or old yellowish hemorrhagic areas are often found in these tumors. Areas of dense and even calcareous tissue are also frequent. Many tumors are found in which a part of all the tissue within the capsule has become liquefied. The contents of such a degenerated cyst are of amber color or hemorrhagic. They practically always contain cholesterin crystals.

The surrounding gland in which these tumors are present presents the same acinar characteristics which have been described above for the symmetric thyroids. In the majority of specimens the surrounding gland is of the colloid and fetal type. The acini do, however, sometimes present a picture of pressure atrophy, which is not seen usually in a symmetric thyroid which is not complicated by neoplasms. One may describe adenomas of the thyroid according to the following descriptive key:

Single or Multiple	Granular Fatty Necrotic Cystic (degenerated) Fibrous Hemorrhagic Calcareous Hyaline	Degenerating	Undifferentiated fetal Simple Colloid Hypertrophic colloid and parenchymatous Hypertrophic parenchymatous	Adenomas in	A. Fetal B. "Normal" C. "Normal" and fetal D. Hypertrophic colloid E. Hypertrophic parenchymatous F. Hypertrophic colloid and parenchymatous G. Hypertrophic fetal, colloid, and parenchymatous	Thyroid

In spite of these anatomic facts and the excellent chemic, surgical, clinical, and pathologic research, which has given us a much clearer idea of goiter, very little is known about the etiology, or indeed the physiology, of the gland itself. New paths of research should be utilized in conjunction with the research which has already been done.

Not until gastric juices had been obtained by means of a fistula were we able to obtain the slightest conception of gastric secretion. Not until then were we able to study the properties of gastric juice and the action of stimuli upon its production. Not until we were able to collect saliva from the salivary ducts were we able to study the chemic and physical properties of its active principle and to control its production by stimulation. These facts are so clear that they make us fear that the truth about the thyroid is far distant.

The field, however, should not be a discouraging one. Indeed, it is filled with the greatest and broadest interest and possibility because it involves something more than experimental surgery and chemistry. It involves, first of all, the discovery of an experimental animal with a patent thyroid duct from which secretion may be obtained. This is the work of a zoölogist or zoölogic physiologist, and his attention should be drawn to his broad experimental interest and practical significance.

Somewhere in the animal kingdom there is probably a thyroid which functionates normally with a patent duct or analogous organ. Whether this animal is aquatic, terrestrial, or both is, so far as the writer knows, still undetermined.

REFERENCES

Oswald: "Virchow's Arch.," 1902, vol. clxix, Habilitationsschrift, 1900, Strassburg.
Schiff: "Rev. méd. de la Suisse romande," 1894, Nos. 2 and 8; "Arch. exp. Path." vol. xviii.
Bircher: "Volkmann's Sammlung klin. Vorträge," 1890, No. 357.
Horsley. "Festschrift, Virchow," vol. i, Berlin, 1891; and "Brit. Med. Jour.," vol. i, 1890, p. 287.
Von Eiselsberg: "Wien. klin. Woch.," 1892, Nos. 5 and 6.
Payr: "Arch. klin. Chir.," 1906, vol. lxxx, Nos. 3 and 4.
Oidtmann: "Preisschr.," Würzburg, 1858.
Chatin: Quoted from von Eiselsberg, "Deutsche Chir.," 1901.
Baumann: "Zeit. phys. Chem.," 1895, vol. xxi, p. 319.
Roos: "Zeit. phys. Chem.," 1896, vol. xxii, p. 16.
Notkin: "Wien. med. Woch.," 1895, No. 45; "Virchow's Arch.," 1896, vol. cxliv, suppl. 224.
Blum: "Berlin. klin. Woch.," 1898, No. 43.
MacCarty: "Amer. Jour. Med. Sci.," June, 1909.
Marine: "Arch. of Int. Med.," 1909, vol. iv.

THE SURGICAL IMPORTANCE OF THE THYMUS

A REVIEW OF THE QUESTION*

CHARLES H. MAYO AND BERNARD FRANCIS McGRATH

OUTLINE

1. Introduction.
2. Embryology.
3. Histology.
4. Anatomy.
5. Growth and Involution.
6. Physiology.
7. Pathology
    - Infections.
    - Syphilis.
    - Neoplasms.
8. Status thymicus—mechanic theory.
9. Status thymicolymphaticus
    - Addison's disease.
    - Exophthalmic goiter.
    - Other associated conditions.
10. Diagnosis.
11. Treatment.
12. Summary.

In presenting this paper, the main purpose which the writers have in mind is to aid in stimulating an increasing interest in the investigation of the so-termed internal secretions of the body, to place abstracts from the authoritative literature before those to whom some contributions may not be easily available; and to lay a stone in the foundation of our own contemplated investigations. Because of the essential importance of this problem in the scientific advancement of medicine, any contribution which may help to stimulate a more general practical interest in it has a reason for its existence. The problem is replete with seemingly unfathomable complexities; consequently scientific progress has been slow, but, viewed in the light of what has already been accomplished, a solution of many practical phases of the subject may be confidently anticipated from serious concerted efforts, of which the medical profession has proved itself capable.

---

* A preliminary paper which is incorporated in this article was read by title before the American Surgical Association, May 31, 1912, and published in the "Annals of Surgery," July, 1912, pp. 77-82.

An undeniable sequence of this problem's solution would be a radical revision of much of the present indefinite symptomatology, aimlessly directed therapeutics, and erroneous designations of the causal factors in death.

In reviewing the rather extensive investigations reported, we find that attention has been focused mainly on the following structures: The hypophysis, thyroid, parathyroids, thymus, pancreas, adrenals, testes, ovaries, the lymphatic and the chromaffin system. Whereas the results of investigations prove these to be very important factors in the complex processes, yet evidence indicates, and it seems plausible to assume, that still other structures of the body are to be considered in this relation. The observed increase of adrenalin in the blood in association with hepatic affections (Kostlivy), and experimental observations on the prostate (Serrelach and Pares), are significant in this regard.

In analyzing the results of experimental, clinical, histologic, and pathologic observations which the literature presents, one cannot but be impressed by the frequent lack of uniformity. For some experimenters to have observed practically negligible ill effects from extirpation of one of these organs, while others noted a train of serious disturbances resulting in death, seems to indicate errors somewhere in the fundamental principles of experimentation. Likewise, in the interpretation of the normal in these structures we see a diversity of views, traceable to a neglect of essential considerations, such as the normal variability of an organ and the exclusion of pathologic effects. Hammar has pointed out this source of error in estimating the size of the thymus, and Hart has shown that this gland is commonly affected by the ordinary diseases of childhood. Disturbances and even death have been positively ascribed to organs whose changes might be merely coincidental, at most contributory, representing but an element in the untoward or lethal process. Again, the findings might be in truth but evidences of a compensatory effort, resulting from a correlationship with the real causative factor.

It is obvious that for accuracy and uniformity of experimental results parallelism of all the essential factors concerned is a sine qua non. As is commonly appreciated, this parallelism includes animal species, litter, period in the functional life of the organ investigated, functional status of the correlated structures, general conditions, etc. Whereas a parallelism of some of these factors is more or less readily attainable, yet it must be admitted that there are others, the determination of which is, at present, fraught with seemingly insurmountable difficulties.

With the object of reducing these factors of error in our future work in this clinic we are endeavoring to rear dogs and other species of animal, aiming at uniformity of breed, age, weight, and other considerations. The work is, as yet, in its infancy, but the limited observations thus far made have sufficiently encouraged us to persevere toward perfecting the plan. Likewise, appreciating the erroneous factors which are liable to creep into experimental observations through misinterpretation of animal histology, we regularly make complete autopsies, preserving a series of specimens in each case. From the comparative histologic study of this increasing material we hope to establish a base-line, to be reasonably able to determine the normal and better interpret deviations therefrom. The value of this work in its relation to experimentation is obvious.

With regard to the clinical aspect of this question, it is evident that, in obscure cases, decisions which are based on inadequate examinations and unconfirmed by autopsy are at best speculative, consequently of no statistical value in making deductions.

Moreover, the findings at autopsy may be misleading, as is evidenced by misinterpretation of postmortem changes and opinions based on incomplete investigation. Autopsy is a possible source of error even more dangerous and wide-spread than the clinical diagnosis, since the findings are only too often accepted as the final word, while the clinical opinion may be viewed with skepticism. It is a self-evident fact that, for autopsy findings to be of scientific value, the work must be done by an experienced pathologist, and that the macroscopic examination be supported by an exhaustive microscopic investigation. Unless this point be duly appreciated, much evidence which is essential for accurate diagnosis will continue to remain hidden within the organism.

However, despite their evident indefiniteness, the many observations have emphasized one important fact, namely, that in our investigations of these structures their correlationship in physiologic function and pathologic disturbances must be constantly before the mind.

The association of thymic changes with pathologic conditions has long been noted. As early as 1614 Plater discussed the so-called "thymic death," and reported cases. Since Plater's time numerous contributions to the subject of the thymus have been made. Of the older works, that of Friedleben (1858)—"The Physiology of the Thymic Gland in Health and Disease from the Standpoint of Experimental Investigation and Clinical Experience"—is one of the most comprehensive. A valuable and exhaustive contribution in recent times is that of Hammar (1909)—"Fifty Years of Thymus Investigation." In this "critical review of the normal morphology," besides discussing the various morphologic elements in the thymi of different species of animals, including man, Hammar presents a quite complete bibliography of the subject up to the time of writing. This work seems to be viewed as authoritative, and Hammar is freely quoted by most writers on the subject.

A recent contribution to the question of the thymus, and one which deserves special mention, is that by J. Wiesel. This work is a comprehensive treatise on the subject, and is of particular value, since the author not only cites the various investigations which have been made, and the numerous theories and opinions advanced, but tends toward a practical application of the knowledge at hand. The writers are indebted to Wiesel's work, as well as that of Hammar, Friedleben, Hart, Matti, Tandler, Bartel, v. Neusser, *et al.* To these are added some statistics and observations from this clinic, with the object stated in our opening words.

EMBRYOLOGY

Embryologists agree that in animals the third branchial cleft contributes chiefly to the formation of the thymus. Kölliker, Born, Rabe, and Prenant maintain that this alone is to be considered. But it is also held that, in addition to this principal anlage, a rudimentary outgrowth arises from the ventral wall of the fourth branchial cleft, external to the origin of the lateral thyroid. According to Groschuff, this anlage may persist in man as the parathymus, a small body which occurs in close association with, or even embracing, the parathyroids derived from the fourth pouch. The latter cleft also gives rise to the lateral thyroid anlage. The thymus grows downward in relation to the pericardium. In the early stages of its development the cervical portion incloses a very narrow cavity; the lower part sends forth numerous roundish, solid branches. This branching process continues until finally the entire tubular portion is involved, and the whole organ has assumed its lobular structure. In a pig embryo of 13 mm. Born observed the dorsal and distal end of the third pouch enlarged, and the rest transformed into a very narrow canal, by which the end is connected to the pharynx proper. The thymic duct has been observed to open into the esophagus, the trachea, the mouth, and even the pericardium.

Fig. 186 illustrates the embryologic relations of the thymus—its close developmental associations with the parathyroids and the thyroid. Whatever in truth may be the significance of this topographic relationship in the embryology of these structures it is at least interesting, viewed in the light of the reported frequent coexistence of the enlarged or persisting thymus, together with goiter, and the rôle attributed to the thymus, as well as to the parathyroids, in the causation of tetany. Basch states that the activity of the thymus is very closely united to the function of the thyroid. He notes the close embryologic and anatomic relations of this group of branchiogenic organs. Matti draws attention to this relationship as one reason why, in some cases, experimental thymectomy is not followed by the typical symptom-complex following thymic extirpation.

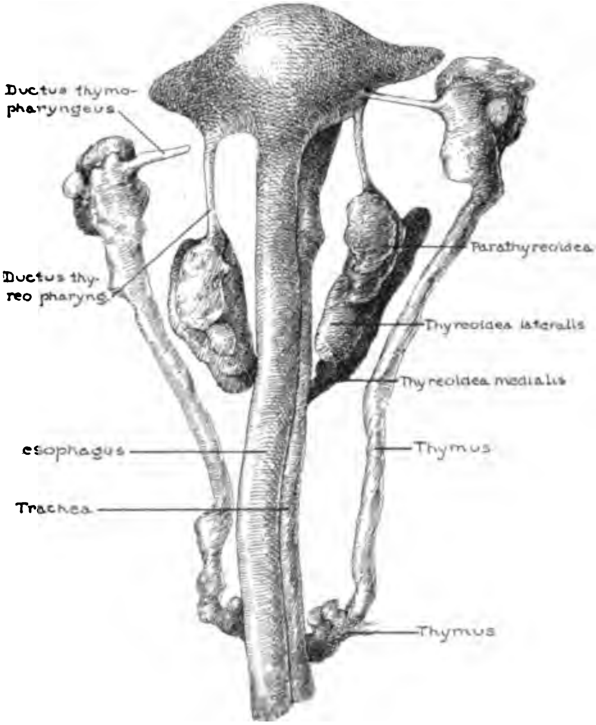


Fig. 186.—The anlages of the thymus and thyroid of a human embryo (18.5 mm.). View from behind (after Kollmann).

Histology

In substance there are two types of cells in the thymus—the reticulum cells and the so-called thymic lymphocytes. The reticulum cells are considered epithelial elements, which result from a direct transformation of the primary thymic anlage, and during the entire existence of the thymus preserve their epithelial character. Both the concentric Hassall corpuscles and the single-celled Hassall structures are to be looked upon as functional differentiations of the epithelial reticulum cells. The cells of the medullary zone are to be reckoned with the reticulum elements. Opinions vary mostly with regard to the small thymic cells. Stöhr believes these to be also epithelial elements from which the reticulum cells are formed. Hammar and Maximow, on the contrary, look upon the small thymic cells for the most part as typical lymphocytes, which secondarily invade the epithelial anlage and obliterate its character. Hammar says: "The thymus is an epithelial organ, which is permeated with lymphocytes." Prenant and a few other writers have held the opinion that a part of the epithelial cells of the thymic anlage is transformed directly into lymph-corpuscles and adenoid tissue through repeated division. Barbano maintains that these changes take place through the direct transformation of the elements peculiar to the thymus, that these elements are to be considered as nothing more than undifferentiated connective-tissue elements, which are not only to be compared to, but also identified with, the lymph-cells found in the areas of round-cell infiltration. During their life these cells slowly develop their property of differentiation and form connective tissue. In conclusion this writer states: "In every case the thymus in extra-uterine life is a genuine connective-tissue organ. Of connective-tissue nature are its small cells, the epithelioid cells, the Hassall bodies, and the granular cells arising from these."

Weidenreich states that the cortex of the thymus is proved to be a genuine lymphoid tissue. In his work on the place of origin of non-granular and granular leukocytes the above author maintains that not only the large lymphocytic forms, but also the small typical lymphocytes, can directly become eosinophiles, neutrophiles, and basophilic cells in the thymus. This formation of granular leukocytes from lymphocytes he has repeatedly shown in other lymphoid organs.

Stöhr holds that thymic lymphocytes, like all lymphocytes, have a basophilic protoplasm, and, in amphibia, ameboid movements. He remarks the sensitiveness of all lymphocytes, including those of the thymus, toward *x*-rays. This was first shown by Heineke and Rudberg. Stöhr does not admit Hammar's view, who advanced ameboid movements for identifying thymic lymphocytes with lymphocytes in general, since these movements are not a specific peculiarity of those cells. Schäffer's finding that there is a transformation of the small round-cells of the thymus into plasma cells is considered to be the surest proof of the genuine lymphatic nature of the small thymic cells. Laurell concludes, from his work on intrathymic and extrathymic lymphocytes, that the noted difference in size is only accidental—that there are no grounds for separating the two. The chemic studies by Bang and Ritchie indicate the same result. Syk has found that the number of mitoses in the thymic cortex of the rabbit during the first six weeks of life is nearly eight times that of the medulla. Larrier, Letulle, and Nathan observed in the rabbit's thymus a number of basophilic elements from which arise amphophilic myelocytes. It is said that these elements have their origin in the thymus itself. Eosinophilic cells were first described in the gland by Schäffer. These have attracted considerable attention. Schäffer found them in the human thymus from the thirteenth to the fourteenth week onward, Pappenheimer, even in the third month, and Stöhr, in the fifth month. Dudgeon observed eosinophiles in children and young animals, but never in adults and old animals. These cells are mostly perivascular, but also intravascular and in the parenchyma itself. The normal presence of eosinophiles in the thymus is caused by the chemotactic influence of the degenerating epithelial cells of the Hassall bodies (Mensi, Ehrlich, and Lazarus). If in the infectious diseases of children bacteria be found in the thymus, eosinophiles are either absent or sparse. On the contrary, non-infected thymi contain strikingly large numbers of them (Mensi). This the author interpreted as negative chemotactic influence of bacterial toxins upon eosinophiles. Schäffer held these eosinophiles for phagocytes, because of their numerous presence in involution and their granulations for degenerative products. Pappenheimer's view is quite contrary, namely, that the eosinophilic granules designate a definite stage of secretory activity, as is similarly observed in the hypophysis and the parathyroids. In other words, this investigator believes in the possibility of these cells possessing a particular function. Rudberg noted, from the use of x-rays, an invasion of pseudo-eosinophilic cells synchronously with the destruction of the small cells. Plasma cells have been observed in the involuting thymus (Schäffer, Ronconi). Red blood-corpuscles are not infrequently found lying free in the parenchyma. The thymic reticulum is described as an almost purely cellular structure. Besides this there is a reticulum composed of connective tissue. Hammar says that the fibers of the reticulum have not been duly separated—that there are fibers genetically and microchemically different. Some are genuine connective tissue and others are formed within the epithelium, and the latter are to be compared with the glia-fibers of the central nervous system or with the Kromayer fibers of the epidermis. Those arising from connective tissue form the adventitia of the larger and smaller parenchymatous vessels. Prenant noted mitosis of the reticulum cells, particularly in the developing thymus; Hammar in the fully developed organ, also during age-involution, and Johnson, during hunger involution. To Hammar this finding seems to indicate that consumption of the reticulum cells during the functional life of the thymus lies within the range of possibilities.

ANATOMY

The thymus is of grayish-red color, has an irregular, flat, oblong shape, and consists of two usually asymmetric lobes,—lobus dexter and lobus sinister,—united only by a loose connective tissue. Each of these lobes is composed of a large number of small lobules,—lobuli thymi,—which are separable from one another, but are all connected by a medullary cord,—tractus centralis,—which follows a tortuous course inside the thymus. The gland lies just behind the sternum, in the spatium mediastinale anterior; it is bounded behind by the upper part of the pericardium, the vena cava superior, venæ anonymæ, the arcus aortæ and its branches; laterally and partly in front by the pleura mediastinalis. Above it may reach behind the musculi sternothyreoidei as far as the glandula thyreoidea. Its anterior wall is loosely, the others more firmly, connected with the surrounding tissues. The thymus is described as attached to the thyroid by the thyrothymal or suspensory ligaments.

GROWTH AND INVOLUTION

An important chapter in the discussion of the thymus, and one in which the results of investigations and the views are considerably divergent, is that of growth and involution of the gland. Among other considerations it is important, because of its bearing on experimentation and diagnosis. From the observations already made by numerous investigators it seems that the thymus has a limited existence of principal functional activity, and that this is during the early period of life. In its existence two phases are recognized—one of progression, the other of regression. The life of the gland naturally varies in different animals, likewise its function at the different periods of its existence. It is evident that conflicting experimental results must follow failure to appreciate these and similar factors. Lack of knowledge as to the importance of the thymus in later life is a source of confusion in diagnosis. Remnants of thymic tissue are present in adult life, even in old age, more frequently than was formerly recognized, and the gland is noted "persistent" or hyperplastic in association with certain diseases. The significance of thymic "persistence," whether it be a physiologic process, compensatory in nature, or pathologic, causing by itself serious disturbances or contributing to such through a correlationship with other diseased structures, is still a much-debated question.

Hart says there is a physiologic age-involution of the thymus which, apart from pathologic events, is an absolutely constant process, so that the functional power, which Waldeyer and also Hammar assume even for the parenchymatous remains of the retrosternal "fat body," is not the same in every portion of the individual's life—it must be highest during the developmental period of the organism. Some of the views held by various authors: The thymus reaches its greatest weight in the new-born (Collin and Lucien, Bovaird and Nicoll). Involution begins at birth or in the first year (Kaiserling and Orgler). The thymus attains its highest growth toward the end of the second year (Hart, Rolleston, Ruhräh, Hertzig, Vincent, and others). The greatest anatomic development and the most important biologic epoch are to be looked for between the second six months and the third year of life (C. Basch and A. Rohn). Sokoloff concludes, from clinical and experimental studies, that under normal conditions the gland continues to develop until the twelfth or fourteenth year, the maximum increment of growth occurring at the sixth year. In advanced age the thymus is still in evidence. Hammar states: "The organ's normal growth continues to the time of puberty, and not until the tenth or the fifteenth year is the highest point reached." V. Sury, Ronconi, and Riddle are also of this opinion. The majority of investigators, therefore, maintain that thymic growth is present in postfetal life, and the debate is only over the time that this growth reaches its highest point, how long the organ remains, when and how soon the physiologic function is executed.

Barbano, in his contribution on "The Normal Involution of the Thymus," disagrees with Kölliker, His, Henle, Capobianco, Mietens, and others, whose descriptions, he maintains, indicate that they view the entire process of thymic involution as similar to a genuine simple cirrhosis. Basing his opinion on the results of his own work Barbano considers the phenomenon of this involution to be the effect of an active, slow process, which proceeds gradually in all the thymic elements, a process considerably more complex than a cirrhosis, and including in its plan the formation of fat-vesicles, connective-tissue bands, also basophilic granular cells, and wandering phagocytes.

Hart says: "The physiologic as well as the pathologic involution of the thymus depends, in the first place, upon an atrophy of the normally constituting cellular elements. The so-called lymphocytes diminish through emigration; the reticulum cells, on the contrary, in consequence of degenerative processes. . . . The difference between physiologic and pathologic involution rests not alone on the degree and the more or less rapid course of the cellular rarefaction, but also on the dissimilarity of the processes in the connective tissue of the interstices and the surroundings. In the case of physiologic involution there occurs a genuine growth of fat tissue, which can yield at any time to a new formation of parenchymatous islands, while in the pathologic there take place reactive connective-tissue growth and sclerosing, which in all severe cases leave behind irreparable changes in the organ."

The presence of accidental thymic involution was known to Wharton (1659), who observed it in animals after excessive exertion. Later also the importance of chronic diseases was repeatedly demonstrated, and, particularly by Friedleben, it was established that, after a short time, during the withholding of nourishment, not only the total weight, but also the parenchymatous value, is quickly diminished. But, in spite of this knowledge of accidental involution, until recent times these signs have been identified with age-involution, and, consequently, led many investigators into error. The results of all investigations agree on the pronounced sensitiveness of the free thymic elements to *x*-rays. The epithelial portion of the gland proves more resistant and assumes the active rôle of phagocytosis. Rudberg has observed regeneration of the thymic elements after the thymus had been exposed to the *x*-ray. Heineke had already noted relatively rapid restoration of the lymphoid tissue in the lymphatic glands, spleen, and the marrow of bones. Friedleben states that complete regeneration of the thymus can occur, as shown in animals which had been reduced nearly to inanition and then refed to overweight. The question of regeneration after disease has been but limitedly investigated and little discussed.

In 495 patients under five years of age Howland found the average thymic weight 4 to 6 gm. Dudgeon's estimate is 5 to 7 gm., Klose's, 5 to 14 gm.; Sappey's, 3 gm.; Testut's, 5 gm.; Fortescue-Brickdale's, 6.6 gm. at one year. Friedleben states the average at birth as 13.75 gm. For a comparative study of thymic weight the reader is referred to the extensively cited tabulations in J. Wiesel's recent treatise on the gland.

Even from the limited observations above, the difficulty of correctly estimating the thymus is manifest. The size of the normal gland evidently varies within wide limits. It is probable that with the acquisition of a more exact knowledge of the thymus we shall be able to estimate it, not so much by its gross size or weight, as by a scientific determination of its normal, subnormal, or supranormal parenchymatous value. In our decisions on the gland the possibility of accidental involution should be kept before the mind.

PHYSIOLOGY

Many and extensive investigations have been made on different species of animals in an endeavor to learn the physiologic function of the thymus, but the problem still remains unsolved, although the observations of recent times have presented some seeming advancement. The questions which naturally presented themselves to investigators are as to whether the thymus is related to the lymphatic organs or stands alone as a gland of internal secretion. Is it a vital organ, and does insufficiency or excess of its function produce deleterious effects? The fact that the thymus presents a structure from two different germinal layers suggests the possibility of more than one function, but this has not been established. Defective technic in experimental work was the strong factor in defeating the early investigations. Friedleben was the first to experience any success in his studies of this phase of the gland, but the only positive result of his work was the demonstration that the thymus possesses, in a high degree, the power to regenerate. Several years elapsed before these investigations were resumed, and the results of Friedleben's first successors were marked with indefiniteness. In the hands of some the sequence of thymectomy was negative, while others noted signs mostly referable to skeletal and muscular disturbances.

Observations have been made on the toxicity of the thymus. In some of these tests the serum of thymectomized frogs and the extract of thymus were injected, and subcutaneous implantation done. As a result of such experiments, it was held that where the thymus is deficient, toxic substances accumulate in the organism, which, under normal conditions, are destroyed by the thymus. Therefore, an antitoxic function is ascribed to the gland.

The results of tests for the importance of excessive thymic function are considered less satisfactory than those for deficient function. In these experiments the injection of thymic juice, implantation, and feeding of the gland were employed. The results of Swale Vincent, M. B. Schmidt, Olivier, Schäffer, *et al.*, were negative. It is stated that the extracts of other organs act similarly to that of the thymus, consequently the latter is not specific. From his experiments Svehla concludes that, as an accelerator of the pulse and a depressor of the blood-pressure, the thymic extract (also thyroid) acts antagonistically to the extract of the chromaffin system. Klose found that the intravenous injection of thymic extract causes in normal dogs increased irritability. Ssokolow says that the injection of the expressed juice of thymus into animals may result fatally, after causing a fall in blood-pressure and a slowing of the pulse. Feeding with thymic substance seems to have no influence on the general condition, although some changes, for example, of bone, have been noted. Weinstrand and Mayer state that after such feeding there occurs an increased output of uric acid.

In striking contrast to the practically negative findings of some investigators are the results of thymic extirpation observed by Klose, Basch, and Matti. Klose, experimenting on puppies, removed the thymus about the tenth day. Results: No noticeable effects at first; the animals grew and increased in weight like the controls, but the increase was in fatty tissue, rather than muscular. The fat was spongy, pasty. Later the puppies became weak and were easily tired; the bones were soft, and the animals manifested less intelligence than normal. They ate considerable, but without choice, were apathetic, and stupid appearing.

After three or four months they began to fall behind the controls in growth, and showed bodily weakness, especially on the part of the bones. Spontaneous fractures were common, and there was increased irritability of the muscles, with frequent convulsions. Finally, the animals became completely idiotic—ate anything: straw, their baskets, parts of their own bodies, etc. They were thin, with coarse hair, which was later shed, and after six to fourteen months died in coma. Autopsy: The bones showed deficient growth, were soft, pliable, with thick epiphyseal cartilage; the brain was swollen and edematous. Microscopically, the bones presented osteoporosis and overgrowth of cartilage. Chemically, calcium, 32.34 per cent.; controls, 65 per cent.

The recently reported experimental work of Matti on dogs presents interesting data. The author's observations are extensively illustrated. Excepting a small number of cases in which the results of thymectomy were negative with regard to influencing the general condition and changes in the skeleton, Matti noted the following: After a varying latent stage, during which only a retardation of the weight-curve, as compared with the controls, is established, there occur increasing drowsiness, easy tiring, evident muscular weakness, and changes of the skeleton, which are very similar macroscopically to those observed in rachitis. From advanced skeletal softening and muscular weakness locomotion is finally much disturbed. Later there occurs an evident stage of cachexia, which leads to death. A genuine idiocy was not noted in these thymectomized dogs. The picture of thymipriva is well marked and typical. Matti states that the changes of the skeleton are to be considered as thymogenic, and due, generally speaking, to a deficient power on the part of the excessively produced new osseous tissue to take up calcium. The striking muscular weakness is co-ordinate to the skeletal changes following thymectomy. Morphologically, it is characterized as atrophy with degenerative signs. No points of a relation between the thymus and the blood in extra-uterine life were observed in these experiments. However, the physiologic decrease of the lymphocytes and the increase of the neutrophilic leukocytes occurred later than in the controls, corresponding to the developmental inhibition of the thymectomized animals. After thymectomy there occurs macroscopic and microscopic hypertrophy of the intrasuprarenal part of the chromaffin system. The indications are that this hypertrophy of the adrenal medulla might be of a correlative kind. The thyroid shows slight increase in weight, corresponding microscopically to a hypertrophy. The author states that from his observations there is probably some relationship between the thymus and the spleen, but this will be investigated further. A striking inhibition of spermatogenesis and ovulation after thymectomy could not be established by these investigations. The pancreas is plainly hypertrophied, but accident cannot be excluded as a factor in the finding of a certain increase of the islands of Langerhans in the cauda pancreatis. The hypophysis appears to be relatively larger, although it is small in the stage of cachexia. The relative weight of the liver is high. In one examined cachectic animal there was found decomposition in the brain and spinal cord, which agrees with the findings of Klose and Vogt. Matti concludes, from these observations, that the signs noted must be brought into causal relationship with the removed function of the thymus; consequently, in growing dogs this gland is not a superfluous structure. Compensatory function of related organs and accessory thymic lobes can prevent the occurrence of symptoms after thymectomy. From his work the author maintains that we must consider the thymus, thyroid, and parathyroids as closely related with regard to their function. The influence on osseous growth is so striking that, apart from the intensive injury of the general condition, we must look upon it as the most essential effect of thymic extirpation. However, the normal course of ossification, of growth, as well as of physiologic activity, cannot be dependent exclusively on the function of one organ. Only the harmonic common effect of all these "glands of internal secretion" can support the physiologic course of ossification. The latter view is supported by Sokoloff's observations.

Basch, using 20 dogs, removed the thymus between the third and fourth week. Results: The bones remained longer in the cartilaginous state; there was a greater excretion of calcium from the kidneys and increased irritability of the nerves, and convulsions were frequent.

Klose considers the symptoms following removal of the thymus to be the result of acid intoxication, presumably nucleinic acid, and a deficiency of lime, with resultant changes in the bones and the brain. The same writer says that in the dog the height of thymic activity is from the tenth to the twentieth day, consequently the gland should be removed at this period to study the effects of extirpation.

Bourneville noted the thymus absent in 25 out of 28 mentally weak children. As cited above, Klose observed severe mental changes in thymectomized puppies.

From his experiments on the influence of the thymus on blood formation Seiler notes the following results: (1) Extirpation of the thymus in new-born dogs shows, as a first effect of the operative procedure, a transitory decrease of the hemoglobin content, also of the number of erythrocytes, and, besides, a transitory leukocytosis. (2) Physiologic decrease of the lymphocytes and corresponding increase of the neutrophilic leukocytes occur later in the thymectomized than in the healthy animals. This is evidently an expression of general inhibition of the developmental process produced by extirpation of the thymus. (3) In older animals, where the thymus has been extirpated for months, there is no longer present an abnormal influence on the blood-building organs as a sequence of the removal of the thymic function. The amount of hemoglobin, the number of red blood-corpuscles, and the number of leukocytes, likewise the relative amounts of the individual forms of the latter, are the same in the thymectomized animals, with symptoms as in the healthy controls. Also, the marrow of the thymectomized animals possesses complete power of reacting to pathologic irritations which excite leukocytosis. Schultz's observations in the arbeit of Klose and Vogt agree with these findings.

Hornowski concludes that the thymus and chromaffin system are to be considered antagonistic—the thymus inhibits, the chromaffin system excites, the sympathetic.

In analyzing the data on the physiologic phase of the thymus, although results from the experimental removal of the gland present many contradictions, yet it seems that recent investigations have thrown some light on the subject. The works of Basch, Klose and Vogt, Matti, *et al.*, indicate that the thymic function is concerned in the general process of nutrition, particularly with the ossification of bone, and that, functionally, it is to be considered in relation with the other branchiogenic glands, likewise with various other structures of the body. Evidence indicates that the thymus and the chromaffin portion of the adrenals act antagonistically on the sympathetic. The gland seems to have no direct influence on the structure of the blood in extra-uterine life. With our present knowledge, it is advisable to use caution in the interpretation of signs of hyperthymization. As Wiesel remarks, Nordmann's view that these signs are to be looked upon as the results of resorption, rather than as signs of a specific intoxication, deserves to be given great weight. In this regard Popper's investigations on the influence of thymic extract in clot-formation are interesting. These observations suggest the necessity of examining for vascular thrombosis as a possible cause of the cardiac weakness and sudden death in case of hyperthymization, whether experimentally produced in animals or seemingly present in the case of individuals.

Pathology

Among the conditions which have been observed in the investigations of the pathology of the thymus are: absence of the gland; certain changes which are considered postmortal; the effects of the infectious diseases of childhood, overexertion, starvation; circulatory disturbances; acute inflammatory processes; tuberculosis; syphilis, and neoplasms.

Wiesel states that one of the most frequently met postmortal signs is a hollowing of the thymic parenchyma. Hammar considers this the result of an autolytic process, in which the proteolytic thymic ferment, demonstrated by Kutscher, plays a rôle.

According to some observers, *absence* of the thymus is very rare in the human. Cases have been noted by Bischoff, Friedleben, Clark, and von Sury. Bourneville reported absence of the gland in 25 out of 28 mentally weak children.

Hart (1912), in an impressive paper on "The Pathologic Involution of the Thymus," points out the frequent occurrence of degenerative effects resulting in this organ from the ordinary infectious diseases of childhood. As a result of his investigations the author maintains that in general an entirely normal thymus is rare in early life; that fatty degeneration of the thymic cells is commonly found in infectious diseases; and that this process increases with the severity and duration of the infections. He states that all subacute and chronic diseases with toxic effects, such as congenital syphilis, chronic enteritis, and furunculosis, lead to a high degree of rarefaction of the thymic parenchyma, wherein is found marked degeneration of the reticulum cells. The degenerative fatty process affects only the large cells of the thymus, the reticulum cells, which seem more highly differentiated elements than the so-called lymphocytes. Hart believes that many errors in estimating the thymus have been due to unconfirmed macroscopic examination, which, he emphasizes, should be controlled by microscopic examination. The latter affords a more positive decision as to the specific parenchyma contained in the specimen. To Fortescue-Brickdale belongs the credit for this observation.

Hemorrhages in the thymus are not an infrequent finding. In some of the cases no apparent cause is demonstrable. Conditions which have been observed in association with these hemorrhages are infectious diseases—for example, whooping-cough and measles, hemophilia, phosphorus-poisoning, and syphilis. Pneumococcic infection is most frequently noted in this relation. Hemorrhage of the thymus was noted in a man who suddenly died three weeks after castration (Bonnet's case, cited by Wiesel). Small hemorrhages are often found in the thymus of the new-born, and are sometimes attributed to difficult labor.

Hyperemia, especially of the hyperplastic gland, is mentioned as a frequent occurrence, caused by various respiratory and circulatory disturbances. Some authors state that thymic hyperemia follows ligation of the inferior thyroid artery, and may at times cause serious effects.

Acute inflammation of the thymus has been observed in the presence of various infectious conditions. Among those noted are erysipelas, diphtheria, variola, measles, scarlet fever, and bronchopneumonia. Microörganisms are sometimes found in the smaller vessels, in the form of coccic emboli, and are also frequently intracellular. Steffen observed two cases of thymic diphtheria.

Abscess occurs in the thymus. It may be single or multiple, and, from statistics, it would seem that the condition is most frequently a secondary process. Wiesel says that in a great number of cases there is a confusion of thymic abscess with suppurating lymphatic glands; also that many cases in the literature are to be ascribed to congenital syphilis. Areas of softening, the sequence of fatty degeneration in case of rapid involution, may have been misinterpreted for abscess formation.

Primary *tuberculosis* of the thymus does occur, according to Bednar, Carpenter, *et al.*, but is usually secondary. It most frequently follows tuberculosis of the bronchial glands, general miliary tuberculosis, or caseous pneumonia. Caseating lymphatic glands may cause confusion. Tubercle bacilli have been found in some cases. Diagnosis of thymic tuberculosis is usually made at autopsy.

Syphilis.—According to statistics, the thymus is very rarely involved in hereditary lues. Fürth holds that the gland is early, but rarely, affected with syphilis. In 350 reported autopsies the thymus was found luetic in between 3 and 4 per cent. of the cases. Fischer describes, as the usual form of syphilis in the thymus, a diffuse interstitial inflammation. Besides this, there is found abscess formation. Most writers note the strongly developed connective tissue and a resultant pressure-atrophy; also, especially in congenital lues, the occurrence of cysts and large epithelioid cells. Fürth's findings, also those of Mraček, have led these investigators to the opinion that the thymus can be the only organ diseased with syphilis.

The *Dubois abscess* is an interesting finding in thymic lues. This is a peculiar formation, which, according to Dubois, is characteristic of syphilis of the thymus. In Dubois' typical case a yellowish fluid in very small drops was obtained from the normally appearing gland. The fluid seemed like pus, and was proved to be such under the microscope (cited by Wiesel). Many such cases have been reported. The Dubois "abscess" has been the object of considerable investigation, resulting in divergent views as to the exact nature and significance of the process. In a case of proved congenital lues Chiari made a very careful examination with regard to the genesis of Dubois' finding. The thymus presented numerous cavities, reaching the size of a pea, in which, besides detritus, typically appearing pus-corpuscles were demonstrated under the microscope. The cavities were lined with epithelium in many layers. Chiari concluded, from these observations, that "abscess" is a misnomer for Dubois' finding; that the pathologic process presents nothing else but a *cyst*, and that this arises from an ingrowth of thymic tissue into the concentric corpuscles. Hammar agrees with Chiari. Eberle does not admit that the cavity is produced by an inflammatory process, but maintains that it is a preformed cavity, dating back to the developmental period, and fails to close because the thymus is influenced by the congenital lues present. As a result of the inflammatory process produced by the disease pus accumulates in the preformed cyst, whereby closure of the cyst is made possible. Therefore it is not an abscess in the strict sense, but the filling-up of a previously formed cavity with pus. Schlesinger is against designating the condition either an abscess or a cyst, but prefers to describe it as an inhibitory process of the normal involution. Weisflog, Schlesinger, Chiari, Eberle, *et al.*, are of the opinion that Dubois' finding is characteristic of lues. The occurrence of gummata in the thymus seems to be rare, but some cases have been reported.

Neoplasms.—The literature contains many reports of thymic tumors, but in the light of more recent investigations some of the statistics, especially the older, may be questioned. It is recognized that the diagnosis of a growth as thymic is not always an easy matter. Tumors arising from neighboring structures may be misleading. Letulle states that, in general, all malignant growths of the anterior mediastinum arise from the thymus. Becker maintains that by far the great majority of primary tumors having their origin in this space are thymic if they do not develop directly from the connective tissue or the principal lymphatic glands. The determining points advanced for the diagnosis of thymic growths are position and thymic rests, particularly Hassall's bodies. As indicated above, position is not a very reliable point. The finding of indubitable Hassall corpuscles is evident proof, but the absence of them does not positively exclude a growth as thymic. The gland is affected by both primary and secondary tumors. The primary tumors are, in general, malignant, tend to freely metastasize, and also to involve neighboring structures. Metastasis has been commonly observed in the regionary lymphatic glands, the pleuræ, lungs, kidneys, pancreas, and spleen. An interesting observation is the fact that, even when the surrounding structures are extensively infiltrated, the thyroid and parathyroids show little tendency to metastatic involvement. Thymic tumors grow slowly, and the first signs usually noted are those due to respiratory obstruction. This may occur suddenly or gradually develop. Other signs observed are those resulting from pressure on vessels and nerves.

Classes of Tumors.—A number of thymic tumors are reported in the literature, but recent analyses indicate that considerable remains to be learned about the pathogenesis of these growths. It is evident that tumors of *epithelial origin* are very rare. Some of the reported cases are doubtful. Carcinoma is considered a growth from the reticulum. Some of these are combined with sarcoma, consequently mixed tumors. Others simulate growths of the parotid in structure. In the adult an enlarged thymus with evidences of respiratory or circulatory disturbances should be viewed as possibly malignant. Several tumors of the *connective-tissue* type are cited in the literature. They are much more frequent than the epithelial growths, although their number has diminished under closer analysis. The most commonly observed is the lymphosarcoma. Sarcomas of the thymus may reach a very great size. They are usually of the small round-cell type. Their contour is rather regular, whereas such tumors of the mediastinum and the bronchial glands are always nodular, and appear almost completely formed of connective tissue. Virchow says that thymic lymphosarcoma can very easily involve the pericardium, the bronchi, and the lungs. The opinion has been expressed that some of these tumors are lymphadenomas or lymphomas. *Cysts* of the thymus are found under normal and a great variety of pathologic conditions. Most of the *lipomas* reported are in the older literature. Thus are seen the difficulties surrounding the diagnosis of thymic tumors. As indicated above, the presence of genuine Hassall corpuscles would be a pathognomonic sign, but these are frequently not found. It is evident that most careful investigation is necessary before designating the type of tumor with which we are dealing.

Status Thymicus

Under this caption is considered the subject of thymic enlargement, exclusive of neoplastic growths. The question which naturally presents itself is, does the abnormally large thymus alone cause serious disturbances? Viewed in the light of the many observations which have been made up to the present time, this is a most practical subject, and a problem still not definitely solved.

Some investigators maintain that in the presence of certain clinical pictures the enlarged thymus is the causative factor, acting mechanically; others, that it produces these effects through its excessive or perverted secretion, and still others that the increased size of the organ is but coincidental, bearing no causal relationship to the noted disturbances.

The so-called "thymic death" and "thymic asthma" are the two principal conditions which have been considered in this relation. Those deaths have been considered thymic in which the exitus is rather sudden, the thymic gland found abnormally large, and there appears no other pathologic condition adequate to explain the lethal result. Asthma, especially in children, has been designated thymic in the apparent absence of any cause other than the enlarged gland.

Since attention was first attracted to the possible importance of thymic enlargement, opinions have fluctuated with regard to the mechanic theory—the effect of pressure of the gland on neighboring structures. Some of the older writers strongly advocated this theory until Friedleben advanced his view, based on the examination of 75 cases, in only 7 of which was thymic hypertrophy demonstrated. Those results suggested Friedleben's dictum: "Es gibt kein Asthma thymicum." This view against the mechanic theory prevailed for a long time. In 1862 the question was again revived, when Virchow, in agreement with Hasse, advanced the opinion that pressure effects of the enlarged thymus on the respiration and the circulation are possible. Abelin was the first of the clinicians to oppose Friedleben's dictum, and subsequently evidence accumulated in favor of dyspnea and death caused by pressure on the trachea, bronchi, heart, large vessels, and nerves.

It is obvious that essential, intrinsic evidence for or against the mechanic theory may be gleaned from the topography of the gland under consideration. For this purpose the writers will make use of the investigations of Hotz, Hart, and Kaplan, cited by Wiesel. The thymus lies in the anterior mediastinum and occupies the entire anterior and superior thoracic space. The uppermost surface of the thoracic portion of the gland corresponds to the manubrium and the corpus sterni, from the superior aperture to the level of the third, in many cases even to that of the fifth, intercostal space (Kaplan). In those cases where the thymus extends to the diaphragm, the gland is always hypertrophic. The capsule of the organ is adherent loosely with the sternum and firmly with the pericardium and the sheaths of the large vessels. The glandular surface is covered by the anterior borders of the lung, so that on opening the thorax only a small strip is visible. The boundary between the cervical and the thoracic portion lies in the region of the sternoclavicular articulation. The cervical part, which averages 1 cm. in length, lies on the anterior wall of the trachea, and sometimes reaches up to the inferior border of the thyroid gland. Usually, however, there remains a free pretracheal space (Hart).

The cervical portion of the thymus is united with the thyroid through small but numerous veins. Laterally, from the cervical portion, the common carotid artery and the common jugular vein course on both sides. The thoracic portion of the thymus lies in the anterior mediastinal space, so that the anterior surface behind the left sternal border, from the second to the third rib, comes in contact with the corpus sterni. Occasionally the anterior thymic surface is uncovered by lung and pleura throughout the entire width of the sternal body, so that it immediately adjoins the posterior surface of the bone. Normally, the thoracic portion of the gland extends from the superior border of the sternum to the plane of the sternal ends of the fifth pair of ribs. This division of the thymus lies partly on the pericardium, partly on several large vessels: arch of the aorta, ascending part of the aorta, the innominate trunk, pulmonary artery, superior vena cava, and on the middle half of the left innominate vein, with which vein the gland is particularly firmly connected. After its entrance into the thoracic cavity the right vagus lies beneath the thymus, while the left only comes in contact with the glandular border. The phrenic nerves course laterally from the thymus, the right passing forward, the left backward. The internal mammary arteries are found on the gland and covered by the borders of the lungs. The thymic arteries branch off at the place where the pericardiacophrenic arteries arise. A branch from the inferior thyroidal artery courses on either side to the superior pole of both thymic lobes. In contradistinction to this arterial supply, there exists but one efferent venous plexus. Klose and Vogt remark that in consequence of this condition the thymus, both in form and function, can particularly easily react to disturbances of the main circulation.

Of especial importance is a hollowing of the gland at the place where it borders on the sternoclavicular joint. At this point the right vagus nerve passes, lying on the division of the innominate.

The left vagus and the left inferior laryngeal nerve are in direct contact with the left half of the thymus. At this place are found mediastinal glands, which adhere in part to the nerves. From the fact that the right inferior laryngeal nerve is situated between the concavity of the subclavian arch and the apex of the pleural sac it is excluded, according to Kaplan, from disturbing influences on the part of the thymus. The same author believes that the cardiac branches and the bronchial plexus of the sympathetic can also be excluded from the effects of thymic pressure. The posterior surface of the thymus adjoins the trachea, the carotids, and, more deeply, the innominate venous trunk of both sides. Sometimes the left lobe lies behind this trunk (Farret). Somewhat lower on the right side the gland borders on the innominate arterial trunk, on the left side, the common carotid (von Mettenheimer). Lower it lies on the pericardium, the left pulmonary artery, the ascending aorta, and the right auricle of the heart; still lower it covers the left bronchus, the left border of the esophagus, and can even insinuate itself in between the trachea and esophagus. After displacement it may reach the vena cava superior, or, from

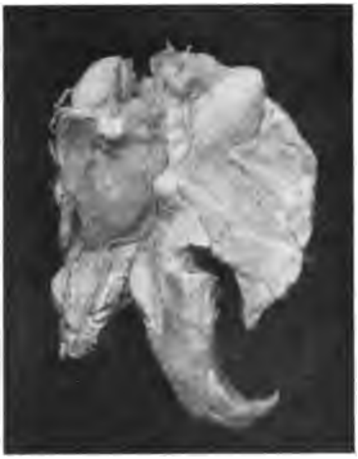


Fig. 187.—Case 49159. Exophthalmic goiter. Thymus weight, 8 gm. Autopsy specimen.

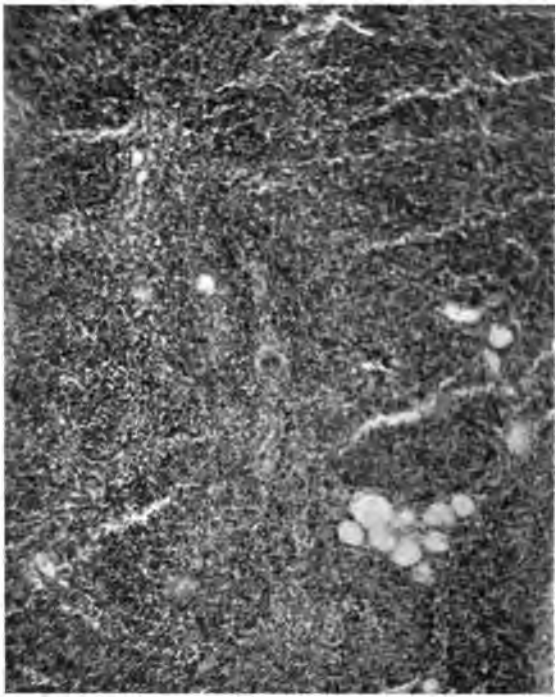


Fig. 188.—Low-power photomicrograph from specimen in Fig. 187.

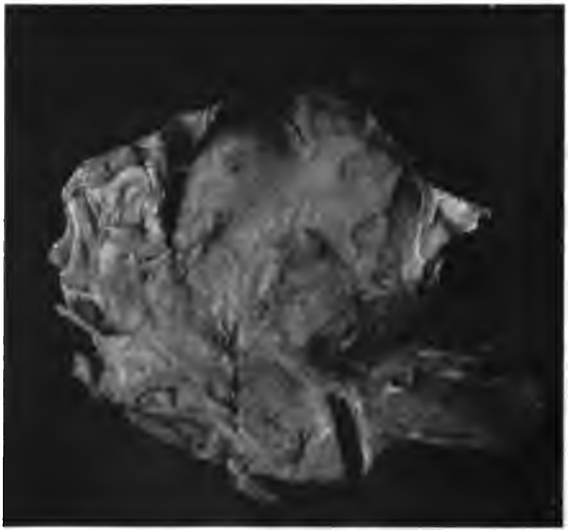


Fig. 189.—Case 40237. Exophthalmic goiter. Thymus weight, 38 gm. Autopsy specimen.

the left, the bifurcation of the trachea. Moreover, the pretracheobronchial glands can be covered by the thymus (Kaplan).

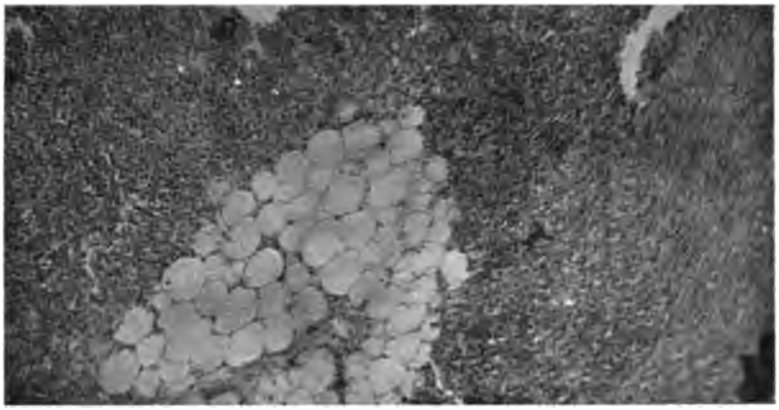


Fig. 190.—Low-power photomicrograph from specimen in Fig. 189.

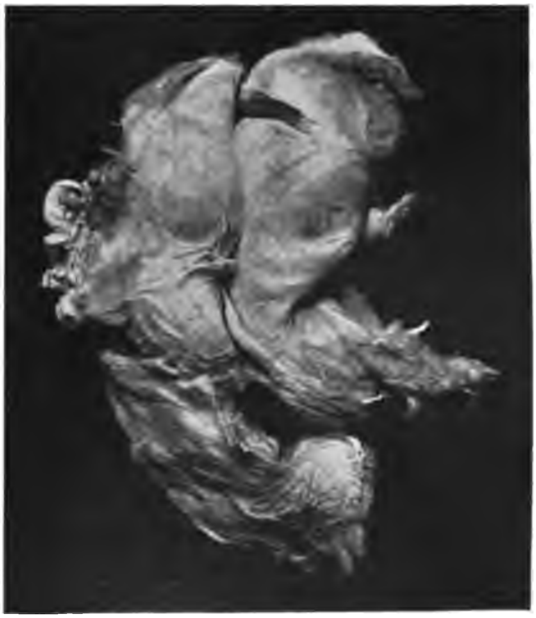


Fig. 191.—Case 41153. Exophthalmic goiter. Thymus weight, 46 gm. Autopsy specimen.

Assuming this to be an accurate description of the normal topographic relations of the thymus in the child, can the abnormally large thymus, acting mechanically, cause the effects attributed to it? The evidence presented consists of clinical observations, investigations at autopsy, results of treatment, especially operative, and experimentation.

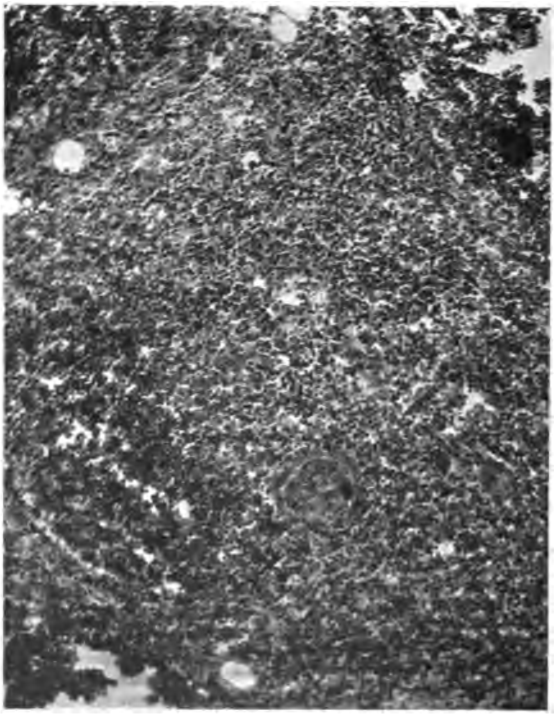


Fig. 192.—Low-power photomicrograph from specimen in Fig. 191.

In the literature are to be found several cases reported in considerable detail. The condition occurs chiefly in the earliest period of childhood. The clinical picture depicted is mainly one of respiratory disturbance, frequently manifesting itself by suffocative attacks. In the beginning the dyspnea may be periodic, but later often becomes continuous, as noted in many of the cases reported. Some of the infants were apparently still-born, but lived a few hours and died from seeming asphyxia. Others presenting no prodromal symptoms were found dead in bed. In still others there were associated diseases, namely, intestinal catarrh, capillary bronchitis, diphtheria, syphilis, rachitis, eczema, etc. The reports indicate that the dyspneic attacks may occur while the child is at rest, but are aggravated particularly by excitement and certain positions, for example, horizontal position, forward or especially backward bending of the head. In some of the reported cases pronounced circulatory disturbances manifested by extreme cyanosis, swelling of the neck, and excessive distention of the cervical veins were present.

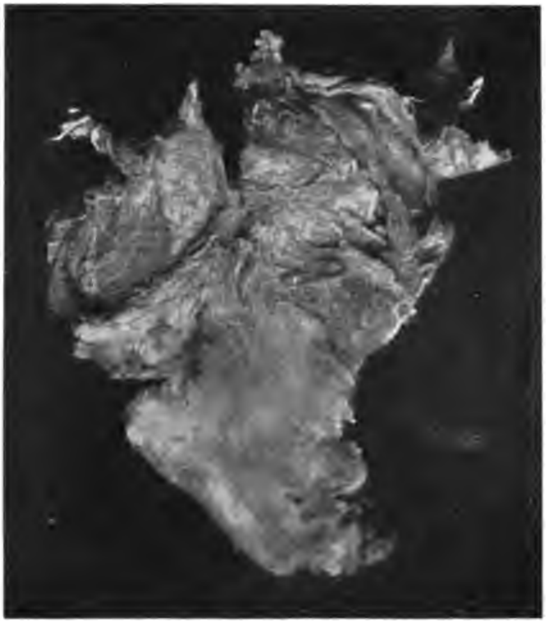


Fig. 193.—Case 43179. Exophthalmic goiter. Thymus weight, 55 gm. Autopsy specimen.

Many of the findings at autopsy have seemed to support the mechanic theory of deleterious pressure of the enlarged thymus on neighboring structures. The most generally accepted effect is that of pressure on the trachea. This tube has been found flattened at different levels. By traction of the head backward the lumen has been greatly narrowed. Some cases are reported in which the flattening occurred where the innominate vessels cross the trachea, and for these it has been considered that the mechanic effect of the thymus was produced indirectly through the underlying vessels. Besides the trachea, the bronchi have also presented flattening in some instances. Pressure-atrophy of the tracheal cartilaginous rings has been reported.

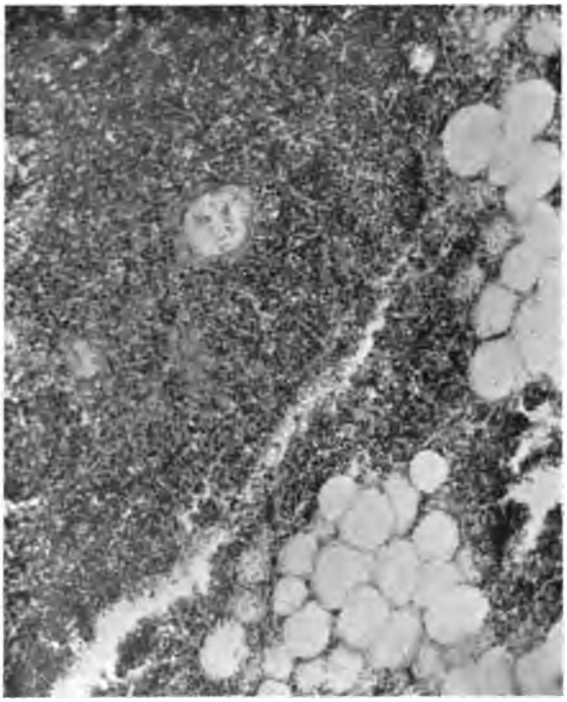


Fig. 194.—Low-power photomicrograph from specimen in Fig. 193.

Illustrative of pressure on the trachea is Feer's case (cited by Wiesel): Age, three months. From the time of birth the child suffered from suffocative attacks. Dulness over the manubrium sterni. Because of this sign it was believed that compression of the trachea occurred through the enlarged thymus. Section proved that at the level of its bifurcation the trachea was embraced and compressed by the thymus. The cartilaginous rings showed pressure-atrophy at the place of compression. This seems to be a typical case, and is the only one admitted by von Sury as positive for the theory of mechanic pressure.

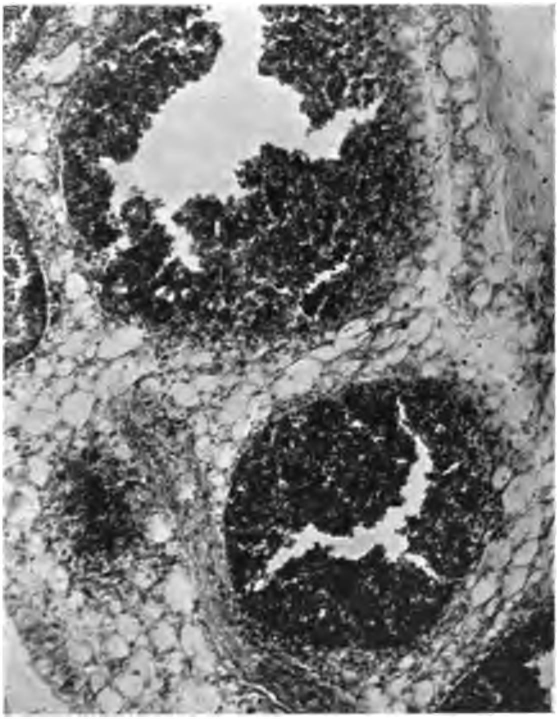


Fig. 195.—Case 41395. Exophthalmic goiter. Low-power photomicrograph from a slightly enlarged thymus.

Purrucker's case may be taken as an example of the operative support to this theory: Age, two years and three months. From the time of birth the child was completely hoarse and suffered from severe dyspnea. By forward traction on the thymus at operation the sound produced through the stenosis immediately ceased, but recurred as soon as the gland was allowed to sink backward. Total thymectomy was performed, resulting in a cure, except that the hoarseness remained uninfluenced.

The following two cases were operated on in the Mayo Clinic (C. H. Mayo):

Case I (A56897).—O. T., male, eleven months old. Dyspnea since birth, seemingly caused by tracheal obstruction. Cyanosis and convulsive attacks at intervals. Frequent vomiting. Unable to sit upright. More comfortable in certain positions and with the head drawn backward. Attacks of coughing which, together with the cyanosis, are less frequent than formerly. Area of dulness over upper part of sternum, extending 3 to 4 cm. to the right, and 2 to 3 cm. to the left, from the first rib to the third. Dulness seemed higher during the backward position of the head—at least there was a slight change in the position of the lower border. *X*-ray shadow (Fig. 196) corresponds to dulness. Operation at St. Mary's Hospital, August 31, 1911. Extirpation of right lobe of thymus. Report of patient, March 7, 1912, furnishes the information that he is developing into a fat, normal child, and learning to walk.

Case II (A77622).—E. E., male, aged three years. General functions normal. Rapid growth of thyroid during past six or seven months, with dyspneic signs suggesting obstructive pressure on the trachea and softening of its cartilaginous rings. *X*-ray diagnosis: mediastinal thickening, probably thymus. Operation, December 30, 1912. Resection, one-half right lobe of thyroid, division of isthmus, removal of left lobe of thymus. Pathologic examination proved the thyroid to be hyperplastic. The portion of thymus weighed 10 grams. Immediately after operation the dyspnea was improved.

Fatal cases with pressure of the enlarged thymus on the heart or large vessels are cited in the literature and seem to support this phase of the mechanic theory. Death has resulted in some of these cases without any apparent obstruction of the respiratory apparatus, and such observations have caused several investigators to sustain this view.

There are also a number of cases reported and opinions expressed in favor of thymic pressure on nerves as a cause of dyspneic attacks and sudden death. Among the authors supporting this theory are König, Rolleston, Pröbsting, Kaplan, Birch-Hirschfeld, and others. Wiesel states that the theory of thymic pressure is the least confirmed.

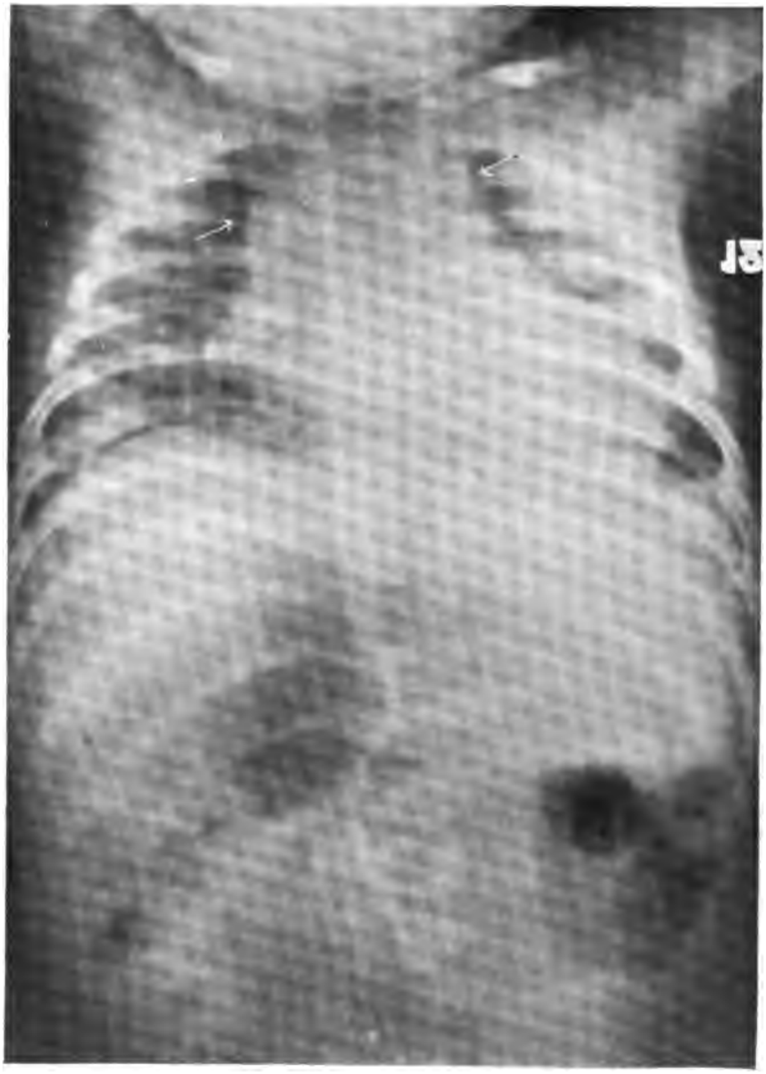


Fig. 196.—Case No. A56397. Enlarged thymus. Confirmed at operation. *X*-ray No. 12820.

Evidence in the form of dysphagia in the presence of an enlarged thymus has been adduced in behalf of the opinion that the abnormal gland can produce disturbances by pressure on the esophagus.

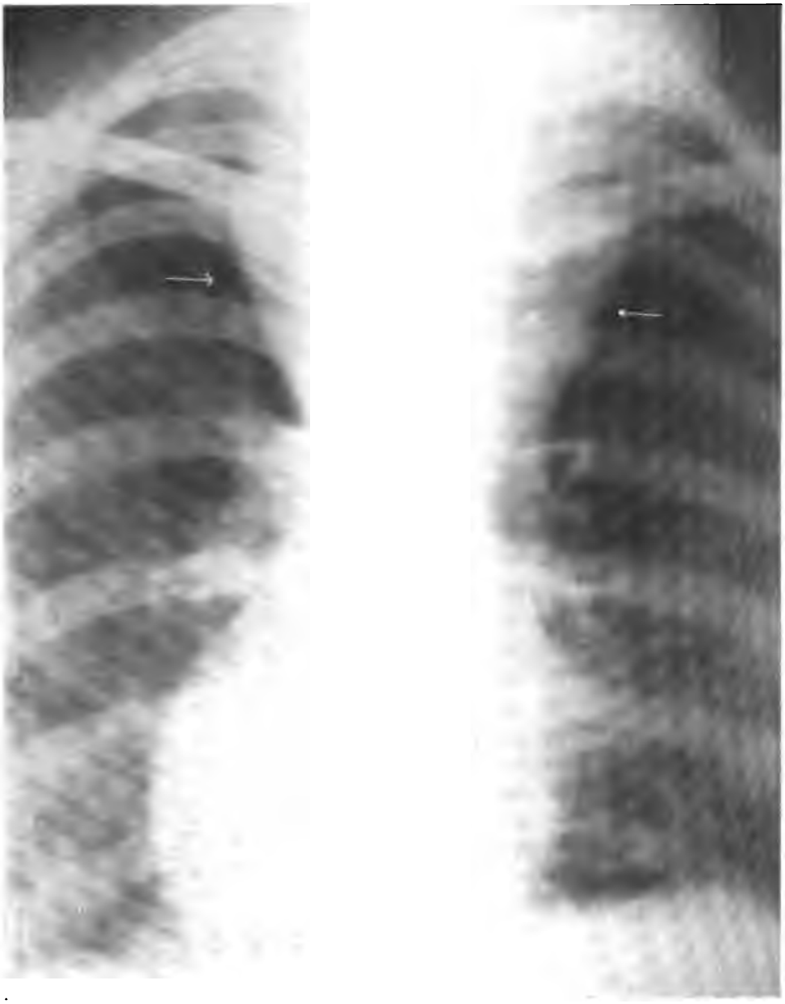


Fig. 197.—Case No. A62264. Intrathoracic goiter. Confirmed at operation. *X*-ray No. 14125.

Despite the numerous seemingly plausible cases cited and the positive convictions stated in the literature on this subject, there are many eminent authorities who strenuously oppose the mechanic theory or at least advise extreme conservatism in making deductions from the mere observation of an enlarged thymus. Von Sury studied the bodies of 2341 children, 82.1 per cent. being nurslings under one year of age. There was not one of these cases which could be termed a thymic death. Hart maintains it must be recognized that in an extremely small number of cases mechanic death by compression of the trachea can be admitted. The same author remarks that thymic death from pressure on vessels or nerves is rather to be assumed when we are dealing with malignant neoplasms.

In by far the great majority of these cases suffocation, produced by thymic pressure, is given as the immediate cause of death. Signs quoted as indicative of a suffocative exitus are ecchymoses of serous and mucous coverings, hyperemia of the brain, fluid blood in the heart, much blood in the lungs, etc. (Grawitz, Beneke, Lange, Clessin, Hedinger, and others). Von Sury opposes these as signs of a suffocative death, claiming that for such a diagnosis observation of the act of suffocation is the absolute proof demanded; furthermore, that ecchymosis occurs more easily in children than in adults, and may be a postmortal development (experiments by Haberda). Hart and Leubuscher do not fully agree with von Sury's view as to the value of these signs, particularly where there are severe clinical symptoms associated with the hyperplastic thymus.

Many authors mention acute swelling of the gland as a favorable factor for compression. Among the causes of such increase in volume are hyperemia, inflammation, and traumatism. It is stated that this acute enlargement of the thymus may result from spasm of the glottis, reflex nervous influences affecting the vagus and causing cardiac inhibition, ligation of the inferior thyroid arteries and veins. Von Sury and Hart are skeptical with regard to the importance of active and passive swelling of the gland.

Kassowitz and several other authors maintain that rachitis is a frequent cause of sudden death; that with this disease tetanic and laryngospastic conditions may be associated. Disturbances and death similar to those ascribed to enlarged thymus have been observed in children suffering from capillary bronchitis, intestinal catarrh, malnutrition, and other diseases, wherein there was either no enlargement of the thymus or there were no signs of pressure by the hyperplastic gland.

From a survey of the field it is evident that the question of thymic pressure is not definitely settled. However, an analysis of the cases which have been reported, together with our own, leads to the conclusion that the gland can act in a mechanic way in causing severe disturbance. That from thymic enlargement alone such effects are infrequent, and sudden death extremely rare, the writers are in agreement with Hart, von Sury, Wiesel, and others. To rest on the mere presence of the enlarged gland in the presence of the clinical pictures which have typified the reported cases is a source of error. Mechanic conditions must be taken into consideration, for it seems evident that the modus operandi, the structure pressed upon, the point and degree of pressure, together with other conditions, are more important factors to be noted than the mere size of the organ. Viewed thus, it is reasonable to believe that a moderately enlarged thymus might be capable of producing disturbances where, in the absence of effectual mechanic conditions, a greatly enlarged gland would fail. The evidence in some of the cited cases indicates, at least insinuates, that as far as the depicted clinical picture is concerned, the thymic enlargement was coincidental—at most, but an element of or contributory to the essential factor causing the severe symptoms or lethal outcome. Its presence may prolong or exaggerate the effects of the real cause.

It must be admitted that most commendable work has been done by the investigators of this subject, but in the light of the combined data it would seem that inadequate clinical examinations, misinterpretation of operative results, and lack of detail in the study of autopsy findings have led to some erroneous deductions with regard to the causative rôle of thymic enlargement in the conditions described. Appreciation of the above points has in recent times stimulated some investigators to undertake fundamental work on this phase of the thymus, and the result has been what seems to be a more scientific advancement in our knowledge of this gland. These investigations are discussed under status thymicolymphaticus.

STATUS THYMICOLYMPHATICUS

An analysis of many clinical observations, findings at autopsy, and operative results indicates that, in the presence of effective mechanic conditions, the enlarged thymus causes disturbances by pressure on certain neighboring structures. However, whereas the theory of mechanic pressure by this gland is admissible, particularly when applied to the early period of life, yet the reported frequency of its occurrence as the sole causal factor seems to be considerably overdrawn. The least tenable of all is this theory as quite commonly applied to sudden death. It is conceivable that the more or less helpless infant, under certain conditions, could suddenly succumb to such thymic pressure alone, but that stronger children or adults would be thuswise affected seems to belong to the exceedingly exceptional circumstances. Lack of laying stress on, or failure in the observation of, coexisting conditions which could adequately explain the clinical picture or lethal outcome, seems to have led to erroneous deductions for the support of the mechanic theory. But in the interpretation of this criticism, or in the practical application of the view which it implies, it is essential to note that the opinion is against thymic enlargement as the *primal causal factor*, acting mechanically, and not opposed to the enlarged gland as a factor contributing, in some cases, to the symptom-complex. The indubitable relief which has been rather frequently observed following operation on the thymus makes it imperative that we duly consider this gland in the presence of some respiratory and circulatory difficulties, especially in children.

Besides the above, there is another very extensive and extremely important class of cases in which the question of thymic hyperplasia or "persistence" plays a serious rôle, and in which also mechanic pressure by the gland is excluded as a causative factor. In this subject are involved complex problems, the solution of which is essential for the advancement of many phases of medical science. Only in comparatively recent times has the subject under consideration been fundamentally investigated, and no discussion of it could be very enlightening without frequent reference to the excellent works of Hammar, A. Paltauf, J. Wiesel, Hart, von Neusser, Kolisko, Bartel and Stein, Tandler and Grosz, and several others.

In many sudden deaths, where the apparently exciting causes were trivial, and also in some serious diseases, thymic "persistence" or hyperplasia has been observed alone or coexisting with certain changes in the general lymphatic system and other structures of the body. These observations have given rise to the expressions *status thymicus* and *status thymicolymphaticus*. Involved in the investigations of this subject is another condition, namely, *status lymphaticus*. Recent macroscopic and microscopic studies support the view of J. Wiesel and others that, at least in adults, status thymicus, status thymicolymphaticus, and status lymphaticus are to be strictly separated from one another.

With regard to the size of the thymus in the three conditions, it has been observed that in genuine status thymicus the gland is generally larger than in status thymicolymphaticus, while in status lymphaticus it is normal or even subnormal in size. It is evident, however, that this observation on the size of the thymus is not an essential consideration in determining the differences in this relation.

Sudden death has occurred in association with various conditions. The affected individuals have been mostly adults, but some cases happening in the earlier periods of life have been reported. Among the conditions under which death occurred are bathing, general and local anesthesia, operations which were frequently minor, flogging, coitus, mental excitement, ordinary walking, and even rest. Some of the fatalities while bathing occurred rather suddenly soon after the immersion, so that the duration of exposure was not a factor. It is quite probable that the diagnosis of "death from drowning" has been frequently made under these circumstances. In most of the cases occurring during anesthesia chloroform was the anesthetic administered, but in some ether was used, while in others local anesthesia in the form of Schleich's solution, novocain, etc., was employed. Death has occurred after but a few inhalations of the anesthetic, at the beginning, during, or a few hours after operation, so that the amount of anesthetic and the duration of anesthesia cannot be depended on as criteria in determining the lethal result in this class of patients.

Among the diseases discussed in relation to the thymic and general bodily conditions under consideration are exophthalmic goiter, Addison's disease, diphtheria, tetanus, eclampsia, eczema in children, myasthenia, osteomalacia, burns, etc. Bartel reports a series of 122 cases of suicide, in 36 per cent. of whom status thymicolymphaticus, in 26 per cent. status lymphaticus, and in 20 per cent. some signs of lymphatism, could be demonstrated. Investigations on diphtheria have shown that this disease is frequently associated with status lymphaticus. In this relation Daut's work in the Escherich clinic has been completely confirmed by Hedinger. The latter investigator also found that most cases of tetanus and quite a few of eclampsia in females showed status thymicolymphaticus. Bernheim-Karrer, von Sury, and others deny the so-called "eczema death" in this relation, holding that the condition here is a septic infection of the blood. Marfan and Halle have observed sudden death in eczematous children, in whom the thymi were normal. The question of exophthalmic goiter, Addison's disease, etc., will be discussed below. Opinions differed as to the cause of exitus in many of these cases. For some the mechanic theory was advanced, but the majority of observers favored the theory of a constitutional anomaly, and this view was substantiated by the findings at autopsy and histologic investigations. "Persistence" or hyperplasia of the thymus was a practically constant finding in these cases. In a few the enlarged gland alone was noted, but usually other changes were observed throughout the body. Among these were a more or less extensive involvement of the lymphatic system and enlargement of the tonsils, the lingual, and the pharyngeal glands. Of special interest is the observation of hypoplasia of the vascular system and the adrenals.

Unable to support the mechanic theory for these sudden deaths, a series of which he attributed to capillary bronchitis, Paltauf, on the basis of anatomic examinations, established the idea of *status thymicolymphaticus*. The important factor in Paltauf's findings is the coexistence of the hyperplastic thymus with enlargements of the lymphatic apparatus. Many of the findings at autopsy, which Paltauf described, had been noted by some of the older writers. Some of Paltauf's observations, particularly that concerning the vascular system, were described by Virchow in 1872 under the title of the Chlorotic Constitution. v. Recklinghausen, Vellemin, and others had also considered the question of a constitutional anomaly. Paltauf's theory was strongly supported by Escherich and his school, also by Friedjung, and later by many others, among whom are Mölders, M. B. Schmidt, Hedinger, Bartel, and v. Neusser. But Paltauf was opposed by others, namely, Richter, Ganghofner, Kassowitz, Rehn, von Sury, *et al.*, and his view was pronounced a hypothesis. J. Wiesel, while maintaining that investigations prove the Paltauf theory to be in essence correct, remarks that the coördination of the thymic enlargement and the hyperplasia of the lymphatic system as characteristic of one and the same abnormal condition meet with serious consideration. It is to be seriously considered because, above all, this opinion has not developed so much from a hypothesis as from objective findings on the cadaver.

The Paltauf theory is particularly applicable to adults. To be emphasized is the difficulty of diagnosing at autopsy these conditions in the new-born and young children. The difficulty here lies in the exact estimation of the size and weight of the thymus. This fact is appreciated by investigators and emphasized by Hammar, who says that such estimation is liable to lead to error, and is of value only in the hands of the experienced anatomist, since the normal size and weight of this gland are variable within wide limits. Misinterpretation of changes in the lymphatic system is likewise a source of danger. This system becomes hyperplastic under the influence of various irritations, as is commonly noted in the intestinal and mesenteric glands as a result of intestinal infections. It is well known that the lymphatic apparatus of the child reacts very readily to such, and the changes in this system may anatomically overshadow the primary inflammation to a great degree. As Kolisko has emphasized, the entire lymphatic structure of the body can become hyperplastic in consequence of rachitis. The same experienced anatomist never saw a single case in which it was necessary for him to diagnose a thymic death, since almost always these sudden deaths could be explained anatomically on the basis of disease of the respiratory and the intestinal tract, or resultant degeneration of the heart. Although advising extreme caution in the diagnosis of a lymphatic constitution from the anatomic findings in children, Kolisko says that in the light of the well-known clinical habitus of the new-born, characterized by pasty appearance, lax pads of fat, paleness, muscular weakness, hyperplasia of the lymphatic system, and a tendency to the exudative diathesis, it must be assumed that also in children there exists a developmental disturbance similar to the lymphatic constitution of adults. Not until after the sixth year does Kolisko diagnose this condition in children, and for diagnostic points mentions the following: The size of the thymus is abnormal for the child's age. There are uniform hyperplastic changes of the entire lymphatic apparatus. Besides these findings, the osseous structure is regular, state of nourishment mostly good, adenoid growths of the pharyngeal and nasal mucous membrane, uniform thickening of the posterior pharyngeal wall, and large lymphatic granulations in the mucous membrane of the entire pharynx and, as a rule, similar granulations in the laryngeal mucous membrane. The hyperplastic changes of the lymphatic apparatus are similar, but more intensive than those observed in the adult.

In adults many points indicating the constitutional anomaly have been demonstrated. These individuals have been noted muscular and powerful (Hart, Wiesel, Bartel, v. Neusser, *et al.*). An entire series of factors have been advanced by v. Neusser, but, as J. Wiesel remarks, these are not to be confined to status thymicolymphaticus alone. Bartel noted them, at least in part, in the *hypoplastic constitution;* Tandler and Grosz, in the *eunuchoid type.* The difficulty of drawing a boundary line between status thymicolymphaticus, the eunuchoid and hypoplastic individuals has been emphasized by Tandler. The factors described are: giant growth, dwarf growth, long arms and legs, large or small head, cranial anomalies, males with feminine anatomic characteristics, as represented in skeletal formation, growth of hair, deposits of fat, etc., and females presenting some masculine peculiarities. The occurrence of these characteristics varies. They may be completely absent or but a few present, and the development only rudimentary. Persistence of the epiphyseal unions is an important finding, noted more often in status thymicolymphaticus, but also present in castrates (Tandler and Grosz). The bone-marrow is frequently red (Hedinger, Bartel, v. Neusser). The changes of the lymphatic structures, which are strongly developed in a number of cases, are important for diagnosis, although all parts may not be affected (Hedinger, Hart, Wiesel, v. Neusser, and Tandler). Wiesel states that in this variation in the extent of involvement is to be noted a principal difference between status thymicolymphaticus, status lymphaticus, and status thymicus. Hart says: "It is positive that the thymus reacts physiologically and pathologically in size and turgescence to irritations which leave the lymphatic apparatus untouched." Bartel called attention to cases in which the hyperplasia of the lymphatic glands is only rudimentary or partial, whereas other signs of the constitutional anomaly are plainly pronounced. The tonsils appear as more or less prominently projecting bodies, consisting of lymphatic tissue, whereas their epithelial crypts are, as a rule, small. The base of the tongue appears grossly granular, the follicles being composed of lymphatic tissue. The pharyngeal mucous membrane contains nodules which may reach the size of a pea. Large follicles are noted in the larynx, chiefly on the inner surface of the epiglottis. The cervical glands are sharply separated from each other, firm, containing, as a rule, little blood, and vary from the size of a bean to that of a cherry. These glands are not embedded in dense cellular tissue. Kolisko points to this as important, since glands which are larger, less definite and embedded in thickened tissue indicate something other than simple hyperplasia, perhaps inflammation, pseudoleukemia, or tumor-like changes. The spleen is constantly enlarged and correspondingly heavy. Its capsule is stretched and may be delicate. There is much blood in the splenic tissue; the cut surface is uniform and often grossly granular, which corresponds to the hyperplastic follicles (Kolisko, Bartel). The findings on the intestinal mucous membrane are inconstant, but, according to Kolisko, this may be covered with numberless nodules, enlarged lymph-nodes, and appear grossly granular. The mesenteric lymphatic glands may also be enlarged. Generally speaking, all the lymphatic glands of the body are increased in size to a varying degree, but most pronounced are the cervical glands (Kolisko).

The enumerated anatomic findings above present the typical picture, but there are a number of cases in which affection of but a single area of the body is demonstrable. For example, only the pharyngeal ring and the cervical lymphatic glands may be involved in the hyperplastic process, while elsewhere the lymphatic apparatus, including the spleen, is small.

In the investigation of this condition the thymus is the most interesting organ. In status thymicolymphaticus and status thymicus this gland is larger and heavier than what corresponds to the age concerned. The thyroid is very frequently enlarged in status thymicolymphaticus, but in genuine status thymicus its enlargement is less constant; in fact, it has been noted subnormal in size (Hart).

In the thymicolymphatic constitution the larynx of the male is small, approximating that of the female in structure, whereas that of the female may simulate the masculine larynx. These peculiarities of the male are also observed in castrates and eunuchoids. Without any evidences of inflammation, diffuse cloudiness of the endocardium of the left ventricle is often observed, due to abnormal distention of this lining, the result of dilating processes and abnormal pressure, which are repeatedly present on the inner surface of the cardiac chambers.

In status thymicolymphaticus narrowness of the aorta is a most noteworthy finding, which is, as a rule, present. A number of reported cases strongly support hypoplasia of the vascular system as related to this constitutional anomaly. The aorta alone may be affected or the hypoplasia may extend to the heart and various branches of the main vessel. Anatomically, this condition presents itself by unusual narrowness, and, together with this, thinness of the vascular walls. The vessels are abnormally elastic. The intima is always delicate, showing occasionally fat-yellow spots. The media varies, is mostly thin, but may be normal in thickness, especially in older individuals. The heart is found small, but is sometimes normal in size or even hypertrophied (Hedinger, Wiesel, v. Neusser). This vascular hypoplasia seems to be absent in status thymicus, but Bartel has noted it in status hypoplasticus.

In status thymicolymphaticus v. Neusser has observed in the lungs abnormal lobulation and bronchiectasis. Often the intestines are particularly long (Bartel). The appendix has been noted long and presenting a pronounced lymphatic structure (Shiota, cited by v. Neusser). The kidneys frequently present embryonic lobulation and cystic conditions. Horseshoe kidney has been observed (v. Neusser), also supernumerary ureters.

The findings on the adrenals seem to be of great importance. Wiesel was the first to direct attention to this condition. The hypoplasia affects principally the chromaffin portion of the organ. Wiesel noted the medulla but slightly developed, poorly stainable, and partly persisting in the embryonic condition. Throughout the chromaffin system the characteristic cells were deficiently developed. The carotid glands were completely absent. This hypoplasia of the chromaffin system has been confirmed in many cases by Hedinger, von Sury, Hart, Bartel, v. Neusser, Goldzieher, Pappenheimer, and Rössle.

These findings on the adrenals and other parts of the chromaffin system Wiesel has observed coexisting with hypoplasia of the arterial vascular system and hypoplasia of the genitalia. Hedinger has made the very important observation that in genuine *status thymicus* the chromaffin system manifests itself both macroscopically and microscopically completely normal, in fact, perhaps extremely well developed. This finding alone justified Hedinger in making the important statement that *status thymicus* and *status lymphaticus* do not present the same conditions. To this Wiesel would add *status thymicolymphaticus.*

The internal and external genitals show deficient or absent development in both males and females. This finding on the genital structures has been confirmed by several observers in recent times. Tandler and Grosz have emphasized this relation, although there appears a great similarity with eunuchoids and castrates. It has been stated that principally in individuals with status lymphaticus or status thymicolymphaticus dysgenitalism is noted. An important fact is that hypertrophy of the adrenals, likewise paragangliomas are commonly associated with premature sexuality. In simple thymic "persistence" without status lymphaticus changes of the sexual apparatus seem to be absent—in fact, such individuals are not infrequently well developed, so far as genitalia and secondary sexual characteristics are concerned.

Among other findings cited in association with status thymicolymphaticus is the tendency of various organs to tumor, especially cystic formations. Such growths have been particularly noted on the ovaries (v. Neusser), on the adrenals (Virchow), and on other structures. Bartel has noted the frequent coexistence of brain tumors, especially gliomas, with this constitutional condition. Cerebral hyperplasia and hypoplasia have been observed in association with persistent thymus. The formerly assumed relationship between rachitis and status thymicolymphaticus is scarcely supported now, although, as Wiesel remarks, signs of lymphatism are frequently to be found in rachitic children. Pfaundler maintains that the exudative diathesis, advanced by Czerny in relation to status thymicolymphaticus, is an accidental involvement of the thymus and the lymphatic glands. v. Recklinghausen cites a case to show the important combination of osteomalacia with this constitutional condition.

Fibroplastic polyserositis has been observed in some cases of status lymphaticus. Adhesions of the pericardium with the heart have been noted. v. Neusser considers this the sequence of a particular tendency to sclerotic inflammation. Bartel observed this tendency of hypoplastic organs to fibrous induration.

The combination of status thymicolymphaticus with changes in other organic systems has been observed in *Addison's* disease. The older writers noted some of these associated changes. In recent times Wiesel and, later, v. Neusser, have stated the opinion that individuals with the status thymicolymphatic constitution, also hypoplasia of the chromaffin system, are predisposed to the development of primary (v. Strümpell, Bittorf) Addison's disease. Therefore it is held that status thymicolymphaticus, Addison's disease and hypoplasia of the chromaffin system have a causal relationship. This view is supported by the observations of many excellent authorities. Wiesel states that this finding in Addison's disease throws important light on the correlationship between the thymus and both adrenal systems, wherein is pointed out the coincidence of *status thymicolymphaticus* or *lymphaticus* and *hypoplasia* of the *chromaffin system*, on the one side, and, on the other side, the coexistence of pure *status thymicus* with *hyperplasia* of the adrenals, as Hedinger has emphasized. According to Wiesel's experience, the adrenal hypertrophy in case of pure status thymicus is above all limited to the *epithelial* portion of the adrenals, and the author considers this at least as a support for the view that *status thymicus* and *status lymphaticus* are fundamentally different subjects.

The following case recently observed in this clinic may be of interest in this relation:

CASE A77836.—H. T., female, aged fifty-five years. Married. Admitted to clinic December 30, 1912. Personal history: Never strong; goiter about eight years; has had children; menopause at fortieth year. Operated on six years ago for pelvic trouble. Followed by fair health for three years. Then in hospital again.

Symptoms: vomiting, nervousness, tremor, diarrhea, palpitation, dyspnea. Improved very much and did work until three months ago, when patient began to lose strength, had marked tremor, urgent dyspnea, palpitation, loss of weight and strength. Nausea, but no vomiting nor diarrhea. In bed most of time because of weakness. Since arrival intense bronzing of skin; complains much of abdominal pain. Excessive bronchial secretion which she is too weak to expectorate. Great discomfort and sleeplessness. Heart dilated and systolic murmur developed during last ten days. *X*-ray chest: heart slightly dilated.

Urine: Specific gravity, 1019; reaction, acid; albumin, trace; sugar, negative.

Blood: Number of leukococytes, 8200; polymorphonuclears, 79 per cent.; small lymphocytes, 14.3 per cent.; large lymphocytes, 3.7 per cent.; transitionals, 2 per cent.; eosinophiles, 1 per cent.

Patient died January 30, 1913.

Clinical diagnosis: exophthalmic goiter—Addison's disease (?).

Autopsy findings: Hyperplastic thyroid; weight of thymus, 30 gm.; extensive bronchitis, dilated heart with myocarditis; liver enlarged and showing much fat; spleen enlarged, and showing some fibrosis; pancreas presents nothing special; adrenals degenerated; genitals negative, although uterus appears very small.

Myasthenia gravis has been noted in association with thymic hyperplasia. Weigert was the first to observe muscular infiltration in this disease. In the myasthenia and other muscular signs frequently occurring in exophthalmic goiter the same has been noted. Wiesel believes that thymic hyperplasia also plays a rôle in the adynamia of Addison's disease. The peculiar infiltration in muscle examined by Weigert presented a structure which completely simulated that of the thymus. Hassall bodies were absent, but Weigert shows that on metastatic thymic tumors these corpuscles are never present. Weigert did not consider the thymus simply hyperplastic in Laqueur's typical case of Erb's disease. In his opinion it was a tumor of the gland. Cases of lymphosarcoma of the thymus, with Weigert's muscular infiltration, have been reported (Oppenheimer, Heer). In 13 cases of myasthenia the thymus proved to be abnormal. Myasthenia has been observed with other conditions, namely, tumor of the lung (Goldflam), right kidney (Oppenheimer), dermoid cyst of ovary (Dreschfeld). Fajerstajn even maintains that all individuals who die from mors thymica are myasthenics. Cases are reported of status thymicolymphaticus in association with acute and chronic lymphatic leukemia. Herz says that such changes are never present with myeloid leukemia.

A very important consideration is the reported association of status lymphaticus or status thymicolymphaticus with both the so-called simple and exophthalmic goiter. Not infrequently in childhood hyperplasia of the thymus is found coexisting with an enlarged thyroid. Birnbaum states that in Switzerland children are born with enlarged thyroids and thymi. The same has been noted in animals by Marine and Lenhart. A large series of autopsies has shown the combination of thyroid enlargement and thymic persistence. It has been estimated that 50 per cent. of individuals with status lymphaticus present enlargement of the thyroid, simple or otherwise. The common combination of thymic "persistence" and exophthalmic goiter has long been known. Joffray is of the opinion that "persistence" of the thymus is found almost exclusively only in cases of Basedow's disease. Lasvenes considers the persisting thymus an accessory fact without importance. Thorbecke noted the coexistence of exophthalmic goiter with enlarged thymus 36 times. In 17 goiter operations, including ligations, partial or complete thyroidectomies, 12 patients died very soon after operation. The deaths were cardiac. Two of these patients died during operation. In 60 autopsies on individuals with exophthalmic goiter Capelle found thymic "persistence" or hyperplasia in 79 per cent. Forty-four per cent. died of intercurrent diseases. During or directly following operations for goiter 22 died. The deaths were cardiac, and 21 (95 per cent.) had persistent thymus. Rendu believes that without exception the deleterious results after operation, likewise the sudden deaths, are to be found in those cases of exophthalmic goiter which are combined with thymic "persistence." Similar results have been reported where the combination was simple goiter and persistent thymus (Rössle). Capelle concludes, from his analysis of this combination, that the presence of thymic tissue is a matter of concern; that it works in some unknown manner, and that the thymus is an indicator of the severity of the case. The author adds, an enlarged Basedow thymus is, so to speak, pathognomonic for a weak Basedow heart.

The surgeons, Rehn and Tillmanns, maintain that in exophthalmic goiter the persistent thymus plays a particular rôle, while Kocher and Riedel defend the opposite view.

Gebele explains the post-operative cardiac failure in case of Basedow's disease to be due to abnormally increased and perhaps perverted internal secretion of the thymus, and maintains that exophthalmic goiter should not be operated on unless the abnormal thymus be previously removed. Gierke states that the majority of deaths after operation for exophthalmic goiter seem to occur in patients with persistent thymus. Zesas thinks it possible that the enlarged thymus, rather than the thyroid, should be the gland removed—at least, thymectomy should precede thyroidectomy, and the operation should not be deferred until the heart has been injured beyond repair by hyperthymization. Matti states that his work, on a greater scale, confirms that of Capelle; that by the activity of the enlarged thymus the Basedow symptoms are evidently increased, the disease-picture, more severe. Matti also supports the works of Wiesel and Hedinger with regard to an insufficient development of the chromaffin system as an associated cause of the unfavorable course of many cases of Basedow with thymic hyperplasia. Petren and Tharling state that the importance of the thyroid's function for the disease-picture of morbus Basedowi is sufficiently established, but hold that it has not been proved that the thyroid is the primary or only causal factor. They believe that future study of the thymus and the adrenals is an essential problem in this affection. Garré has advanced the possibility of thymic hyperplasia being the initial condition in exophthalmic goiter. The results of combined operative therapy are awaited with interest. It is remarked that, from the investigations already made, there seems to be some reason for considering primary thymectomy and eventually trying a preliminary treatment with adrenalin. When in these cases thymic hyperplasia can be shown by the *x*-rays, operative indications should be carefully weighed. Ssokolow maintains that death in these cases is *not* the direct result of the enlarged thymus, but is caused by a disturbance of bodily metabolism, of which the hyperplasia of the thymus, as well as that of other glands, is but one manifestation. Thymic death is usually due to a combination of several factors.

Melchior states that in 80 or 90 per cent. of cases an enlarged thymus accompanies established exophthalmic goiter. There is nothing to show that this enlarged gland has any special toxic action, but it is suggested that the status thymicolymphaticus represents a special reaction of the tissues to excessive functioning of the diseased thyroid. Death is never due to enlarged thymus in the absence of other disease. The truth is that the patient has long suffered from the toxic action of the diseased thyroid, seriously injuring the heart, which is liable to fail at any moment. Related experiences confirm the increasing success of operations on the thyroid for exophthalmic goiter, when the disease is not too far advanced. Latest statistics show that an increasing percentage of such patients are being entirely cured or improved by an operation merely to reduce the size of the gland. Lenormant believes that in the present state of our knowledge it is not possible to designate precisely the rôle of the thymus in the pathogeny of morbus Basedowi. At all events, he says, its rôle appears to be much less important than that of the thyroid body. From a therapeutic point of view the establishment of a hypertrophied thymus must not modify the usual course concerning the indications and the choice of operation in exophthalmic goiter.

Interesting is Dwornitschenko's discussion of Gluck's fatal case of thyroidectomy, which patient died in five minutes after the operation. The former says: "The thymus communicates with the thyroid by vessels. In operation on the thyroid the thymus is more richly supplied with blood, since after operation the inferior thyroid artery sends the greater part of its blood into the thymus, whereby the latter organ is now congested. Also, the thin-walled left vena anonyma, which conducts the greatest part of the thymic venous blood and courses between the aorta and the thymus, presses on the resistant aortic wall, whereby a damming of the blood back upon the thymus results."

According to Barbano, Professor Scagliosi noted at autopsy a greater frequency in the persistence and hypertrophy of the thymus in Piedmont than in the southern Italian regions. This observation tends to support the view of Sahli and Mettenheimer, who have expressed the opinion that region can have an influence on the stronger or weaker development of the thymus, which is of interest in comparison with observations on the thyroid.

The above few abstracts from the literature sufficiently indicate the diversity of views which are held with regard to the significance of thymic "persistence" or hyperplasia in association with goiter. It is well established that the coexistence of these two conditions is quite frequent, but the cause of the thymic enlargement and its influence on the course of the disease of the thyroid are far from having been scientifically demonstrated. Here the sources of error are many, among which is the focusing of the attention on the persistent or hyperplastic thymus, to the exclusion of adequate examination of other structures of the body at autopsy. Likewise, deductions favoring the presence of the thymus as the causal factor in deaths following operation on the thyroid are to be carefully considered. From the history of the surgery of the thyroid gland it is obvious that opinions based on a comparatively small number of cases are liable to be misleading, a statement which can be confirmed by comparing the records of mortality in the early and later periods of work by surgeons who have had extensive experience with this gland.

As observed elsewhere, in this clinic the association of thymic "persistence" or hyperplasia with goiter, both simple and exophthalmic, has been noted, although we have not found a percentage so high as some observers. Thus, in a series of 13 autopsies—exophthalmic goiter—the thymus was noted enlarged in 5. The largest of these weighed 55 grams, the smallest, 8 grams. Vestiges of thymic tissue have been commonly observed. Gross and photomicrographic illustrations of these glands accompany this article. Histologic study of the specimens shows the structure to approximate in general that of the child's thymus.

The total number of operations on the thyroid in this clinic during the year 1912 was 1249—mortality, 1.04 per cent. Of 10 autopsies performed, the thymus was noted in 6 and the amount of thymic tissue varied from a vestige to 40 grams. Four of these 6 cases were exophthalmic goiter. Among the diagnoses of the cause of death are acute septic nephritis with pneumonia, pulmonary embolism, myocarditis with parenchymatous degeneration of organs. An analysis of these deaths shows but one case in which the association of the enlarged thymus with other changes attracts attention.

M. P., female, aged twenty-nine. Exophthalmic goiter. Death occurred about thirty-six hours after operation. Autopsy findings: Heart double normal size, dilated, degeneration of myocardium; chronic pleurisy, right side; liver enlarged, and containing considerable fat; spleen triple normal size; nephritis; degeneration in adrenals; weight of thymus, 40 grams.

Of these 1249 operations on the thyroid, 642 were for exophthalmic goiter (thyroidectomies and ligations). The statistics are presented for the reader's consideration in analyzing the numerous investigations, reported cases, and expressed opinions on this subject. To be noted is the quite extensive series of goiter, many of which are exophthalmic, the absence of status thymicolymphaticus as a causative factor in the deaths, and lack of convincing evidence that the persistent or hyperplastic thymus played an important rôle in the lethal results of this series.

But in contemplating these observations and making deductions from them we must consider the statements of some investigators, who remark that, although individuals with status thymicolymphaticus bear infections badly and may suddenly die from even apparently slight causes, yet there are some who reach old age and withstand repeated anesthesia, etc. It may be, as several reliable authorities are inclined to believe, that status thymicolymphaticus is a strongly contributing cause of the severe symptom-complex and exitus in some cases of goiter. However, while holding the mind open to the possibilities of the persistent or hyperplastic thymus in this relation, and welcoming investigations of others, also pursuing them ourselves, toward the solution of the problem, yet we feel, in agreement with many, that neither the results of experimentation nor observations otherwise made have scientifically proved the significance attributed to the thymus by some in its relation to goiter.

A few citations from J. Wiesel's comprehensive memoir will serve to illustrate the speculative status of the question as to the rôle of thymic enlargement in the presence of exophthalmic goiter. One of Hart's cases with symptoms of Basedow's disease showed a persistent thymus as the only pathologic finding. A preparation of this gland was injected into the abdominal cavity of a guinea-pig, and the consequent clinical picture, together with the findings at autopsy, seemed to support this author's opinion, that the persisting thymus gives off material which affects the heart and the vascular system. Hart controlled his experiment with animals on which calf's thymus was employed, and these controls remained normal. E. Bircher transplanted immediately the thymi of two dogs with exophthalmic goiter into the abdominal cavity, and this was followed by symptoms of Basedow's disease. v. Hansemann views the thymus as a regionary lymphatic gland, and, therefore, considers its enlargement as a reaction to the increased activity of the thyroid, with resultant chemicotoxic sensory irritation. Wiesel says that this view speaks against all the recent findings on the nature of the thymus. Hammar believes rather in a reviving of the gland, and reservedly rejects v. Hansemann's theory. Gierke thinks that the thyroid and the thymus are in a certain manner chemically related, so that the pathologic functionating of the thyroid and that of the thymus compensate in a degree. Failure or deficiency of the thyroid effects a thymogenic autointoxication.

Rössle assumes thymic hypertrophy to be correlative. In case of insufficient secretion of the thyroid the thymus compensates with a similarly acting secretion. Basing his opinion on experimental work, Gebele maintains that the increase of thymic substance in exophthalmic goiter is a natural regulating process. The thymus, becoming enlarged under the influence of the diseased thyroid, takes the place of the latter, thus counterbalancing its effects. In the sudden exitus of Basedow's disease, where the thymus is hypertrophied, the death is cardiac, resulting from the poisonous effect of the dominating thyroid secretion. Bircher, supported by Wiesel, attacks this view of intoxication by the thyroid in death from exophthalmic goiter. Hart disagrees with Rehn's theory of sudden swelling of the thymus in consequence of ligation of the inferior thyroid artery, and resultant sudden death from compression of the trachea. As previously indicated, the former investigator, in harmony with Svehla's view, favors, in fatal cases of Basedow's disease, an acute intoxication, with hyperthymization of the organism. The same author advances, in support of this opinion, the bad results of feeding with thymus in many cases of exophthalmic goiter. Capelle and Bayer are of the opinion that the hypertonic impulse in Basedow's disease is due to both thyroid and thymus; that the functions of the two organs seem mutually to advance each other, consequently also their respective poisons and the severity of the case. Honnicke does not believe that goiter is due to the thymus, nor the enlarged thymus to goiter, but that both have a common underlying cause.

For the differentiation and a more practical knowledge of the constitutional anomalies under consideration histologic studies present a fertile field. Thus far some important observations have been made, but it is evident that this phase of the differential diagnosis needs considerable amplification before the subject is clarified. Herein are concerned the histologic differences between the so-termed constitutional and the acquired lymphatism, the changes which are peculiar in the glands and other structures to the various coexisting diseases that have been discussed. For the greater part of our present knowledge in this regard we are indebted to the very commendable investigations of Bartel and Stein, J. Wiesel, v. Wiesner, Pappenheimer, Hedinger, *et al.*

From the observations already made it seems adducible that some lack of uniformity in findings has been due to the relatively limited material at the disposal of investigators.

Bartel and Stein studied numerous cases of status thymicolymphaticus or status lymphaticus. The individuals were of different ages. The writers give in detail the histologic differences of the first and the second period of growth. Among the cases of lymphatism were some which undoubtedly had their origin in infections or intoxications, consequently were of the acquired type.

Generally considered, deficiency in development of the lymphatic channels and the medullary cords is characteristic of status thymicolymphaticus in the first period of growth. In the second period of growth the picture suggests an atrophy of the specific parenchyma of the lymphatic glands. Bartel and Stein explain the pronounced development of lymphatic tissue outside the lymphatic glands as compensatory hypertrophy, which counterbalances the atrophy of the second period of growth. This same explanation is applied to the persisting thymus and the follicular swelling of the spleen. These investigators maintain that the process observed in the lymphatic system is the result of a developmental disturbance, affecting, first of all, the supportive framework. According to their opinion, this developmental disturbance of the supportive framework is parallel with the structural anomalies occurring on other parts of the organism, such as are concerned in the narrowness of the arterial system, hypoplasia of the genitalia, syringomyelia, etc. Bartel holds these findings to be characteristic of the lymphatism which is based on constitutional grounds.

Glandular enlargements following acute infections may cause confusion with status lymphaticus, but the above findings are wanting in the former condition. Bartel views the lymphatism found in association with chronic infections, for example, tuberculosis, in the nature of an immunizing process. Such lymphatism is to be comprehended in the sense of a general reaction, similar in the different injuries, among which infections, intoxications, and autointoxications are to be considered. Consequently, all cases in which the lymphatic glands present merely simple hyperplasia are to be excluded as acquired lymphatism, especially where no signs of hypoplasia can be demonstrated on other structures.

Wiesel is inclined to believe that the thymus presents conditions somewhat similar to those of the lymphatic glands, which Bartel has described, and says that if future studies should prove this to be a fact, Bartel's theory would be further supported. Hammar has shown that a real connective-tissue development is not present in age-involution, and a degeneration of the parenchyma from connective-tissue proliferation does not take place. v. Wiesner has pointed out the tendency of hypoplastic arteries to connective-tissue proliferation. Bartel and Herrmann noted similar changes in the ovaries. In the constitutional condition these are frequently found enlarged and smooth, the enlargement being due to the increase of connective tissue. This thickening of the connective tissue particularly involves the cortex, but is also present in the parenchymatous layer. There seem to be fewer primary follicles, and the vessels at the hilus are frequently thickened, their walls often presenting hyaline degeneration. The cystic formations prove microscopically to be Graafian follicles, which in consequence of the structural conditions do not rupture the cortex. Corpora lutea are rarely present, but scars are more frequent. In these constitutional anomalies Kyrle observed pronounced increase of the connective tissue in the testicles of young individuals. In extreme cases the same process was noted affecting the seminal ducts. The latter appear deficiently developed, the lumen is narrow, and there is a lack of epithelial differentiation. The induration of the connective tissue is here to be considered injurious to the specific parenchyma. In Addison's disease, with atrophy of the adrenals, for which no plausible explanation has been found, there is seen evident increase of the connective tissue within the adrenals, and rarefaction of the specific glandular portions. Wiesel is of the opinion that this "atrophy," which is seen in many cases of Addison's disease, is a process similar to that described by Bartel and his co-workers for other organs.

The same author states that if the above findings be confirmed, an essential point for the recognition of genuine constitutional status thymicolymphaticus will have been gained. It is a predisposition to hyperplasia of the connective tissue, the demonstration of which would be an important diagnostic factor in differentiating the *constitutional* from the *acquired* type of lymphatism. There are many observations to support this finding, namely, the examinations of Bartel and his co-workers, the combination of polyserotitic and cirrhotic processes with status lymphaticus, likewise Wiesel's view on the so-termed primary atrophy of the adrenals in Addison's disease. But, as Bartel warns, a decision must not be made from the examination of one organ. When a rudimentary development of fibrosis is detected, it is essential to investigate an entire series of organs with regard to their content of connective tissue.

From an analysis of the investigations of Hammar and Bartel, and the observations on his own cases, Wiesel states that in genuine *status thymicus* the hyperplasia of the epithelial elements greatly exceeds that of the lymphocytes. Hassall's corpuscles are present in great numbers,—much greater than usual,—and this is likewise true of the remaining epithelial elements, so that the entire thymus presents a more extensive epithelial structure than otherwise. Consequently the medulla is particularly hyperplastic, while the cortex appears rather diminished. The latter is possibly a sequence of age-involution, since simultaneously the cortical lymphocytes are rarefied. In the same writer's cases of *status thymicolymphaticus* the thymic picture was essentially different from that of status thymicus. In the uncomplicated cases of the former there was a mixed hyperplasia, consequently an involvement of both the thymic lymphocytes and the reticulum. There were no degenerative signs on the Hassall bodies, and fatty degeneration was absent. Active mitotic increase was noted in the lymphocytes. In a case of *Addison's disease* and *status lymphaticus* Hart observed the thymus entirely lymphoid. Pronounced signs of lobulation occurring in age-involution were not evident. The condition of the lymphocytes suggested proliferation rather than persistence. Hassall corpuscles were very sparse. The description of Pappenheimer's first case is similar to that of Hart; there were few Hassall bodies and some of these were necrotic. In Pappenheimer's second case the thymus consisted of irregular lobules, which, sharply defined, were separated from one another by much fatty tissue. The cortical and medullary limits were ill defined. Here and there the cells were arranged like follicles. The nuclei appeared broader, possessing an evident nucleolus and a nuclear membrane. Between these cells lay reticulum cells, showing processes and pale, oval nuclei. The Hassall corpuscles were sparse, hypertrophied, and presented a fibrillary structure. Mast-cells were numerous, and oxyphilic cells were also found. Impressive was the abundance of connective tissue, in the presence of the extraordinary cachexia and atrophy, which the patient presented. In *exophthalmic goiter* the thymic picture is different. The gland presents a histologic structure similar to that seen in small children. The hyperplasia is quite uniform, affecting both the epithelial and the lymphocytic elements. Here there is complete persistence of the thymus, with primary or secondary enlargement, which may have its beginning in childhood. In genuine *status lymphaticus,* both in children and adults (Wiesel), the thymus can correspond to the age, without taking part in the hyperplasia of the lymphatic glands. However, occasionally, and especially in children, there is found a predominance of lymphocytic hyperplasia over that of the epithelial elements.

From this limited review of the investigations of others it can be seen that in status thymicus, status thymicolymphaticus, and status lymphaticus, as well also in certain diseases coexisting with one or the other of these conditions, the thymus presents differences of histologic structure, the careful study of which is essential for the differential diagnosis. It is evident, however, that the present status of our knowledge in this regard is not exact. There still remains much to be explained, but with increasing experience and more general scientific application along these lines an essential, practical advance seems assured.

Diagnosis.—In some cases the clinical diagnosis of an enlarged thymus is necessarily difficult. Usually the gland is not greatly increased in size, and must be rarely palpable. Occasionally one may feel the thymus if the patient be placed in the prone position and palpation made in the suprasternal notch.

Opinions as to the value of the Röntgen-rays vary, some holding that the gland can usually be demonstrated with the radiograph, others that this means of diagnosis is doubtful or of no use. L. D'Oelsnitz gives a number of points in röntgenoscopy. He first eliminates mediastinal lymphadenitis. The author states that the shadow of the normal thymus is no wider than the shadow of the sternum and vertebræ. Any increase in the shadow toward the left should suggest an enlarged thymus, confirmed by the sharp outline. Abnormal shadow of the thymus was noted in 2 of 13 infants, which were a few days old. C. Basch and A. Rohn, using Röntgen rays, employed various methods on dogs and children, but were unable to find in the radiograms any marks which could be definitely considered shadows of the thymus. These writers have resorted to auscultation-percussion. Basch constructed an instrument which duplicates the mechanism of the percussing finger, but is lighter and can be used easily with one hand. It touches only a quarter of a centimeter of the surface, and can be moved easily across these small areas laterally as well as longitudinally. With this instrument he was able to obtain a more definite and exact outline of the anterior thoracic organs than by earlier methods, such as the finger. Basch finds, by direct and auscultatory percussion, an area of dulness somewhat larger than the triangular area depicted by Blumenreich, and outlines the lateral areas of the thymus by the so-called friction method, described by Bianthi and A. Smith. No positive thymic dulness could be demonstrated after the fifth year. A systematic examination of 140 cases seemed to prove that the size of the thymus varies according to the age of the child, its nutritive condition, and to certain pathologic states. Basch and Rohn described the normal thymic area of dulness as of rhomboid form, extending down to the second or third rib, with lateral borders confined to the sternal or parasternal lines. The clinical drawings are confirmed at autopsy. Park and McGuire maintain that, from anatomic study of autopsy cases, the methods of percussion of the thymus based on the theory of thymic mobility, are founded on a false anatomic hypothesis.

L. D'Oelsnitz describes the clinical signs of hypertrophy of the thymus as follows: Puffy and pale aspect, cyanotic complexion, persisting or intermittent, or merely a bluish tint around the mouth. The veins are more prominent than usual; the eyes a little staring or protruding. Such children are sluggish; the fontanels are sometimes tense. In the absence of meningeal reaction this seems to be a sign of considerable value. Like the other signs, it indicates some disturbance in the return circulation. Respiration may be labored; there may be a suggestion of stridor, which becomes accentuated as the child reclines. In one case the stridor came on as the child sat up. These minor signs are fleeting and variable. The diagnosis is sustained by the unusual extent and intensity of the dulness over the manubrium toward the left and the Röntgen-ray findings.

The significance of thymic persistence or hyperplasia alone in association with exophthalmic goiter is at least a question, but the demonstration of the enlarged gland, where evidences of lymphatic hyperplasia and signs of hypoplasia on some structures, such as the adrenals, genitals, and the arterial system, manifest themselves, is a matter of essential importance. The various anomalous conditions indicating status thymicolymphaticus have been cited above under this caption. From the rather extensive statistics indicating the serious rôle of this condition in the lethal result of many diseases, exposure, shock, anesthesia, and operation, and the reported observations of its coexistence with goiter in several cases, it is imperative that evidence of status thymicolymphaticus be carefully sought in the examination of such individuals.

The blood-findings in Basedow's disease have attracted attention in recent times. In a case of this disease associated with typical status thymicolymphaticus von Neusser found 50 per cent. lymphocytes. Schridde states that the lymphocytosis in exophthalmic goiter is dependent on status lymphaticus and not thymic hypertrophy. A lymphocytosis above 40 per cent. is designated by Van Lier as a contraindication to operation for exophthalmic goiter. As an aid to diagnosis, Capelle suggests a test-feeding with a thymic preparation, since, according to Thorbecke, the administration of this gland in a case of Basedow's disease with coexistent enlarged thymus causes evil effects. Consequently, if such patient becomes worse, it is assumed that thymic hyperplasia is present.

It is evident that, with our present methods, diagnosis of thymic enlargement meets with many difficulties. Asthmoid and similar respiratory attacks in young children should not fail to direct our attention toward this gland; the clinical signs of thymic hypertrophy, which have been noted, should be looked for, and the suggested methods of physical examination and the Röntgen-rays employed. Although results from the use of *x*-rays have been rather contradictory in the hands of different investigators, yet with increasing knowledge and perfection in technic it seems that this should be a source of great aid in the diagnosis of thymic conditions.

Investigations of the blood as to its diagnostic importance in the relation briefly mentioned above have not been sufficiently extensive to support a positive opinion; still this is a field which deserves careful exploration. And so, too, with regard to other diagnostic tests that have been limitedly applied. Their importance is at the present speculative, but they insinuate a line of scientific clinical endeavor which may be the foreshadow of fruitful results.

Treatment.—The various modes of treatment recommended by different authors for enlarged thymus are medical, by *x*-rays, and operation.

Schwinn holds that the treatment is mainly medical—by arsenic, mercurials, tonics, air, light, etc. The *x*-ray treatment, he says, has not yet given definite results. Operation is indicated in abscess, and tracheotomy may be required in case of simple enlargement of the gland.

Opinions vary as to the value of treatment by *x*-ray. Rudberg states that *x*-rays cause a very energetic injury of thymic tissue.

But this same author, supported by Wiesel, believes that a lasting success is quite excluded. Friedländer and Myers induced retrogression of abnormally large thymi by this means. Bordate notes that microscopic findings in cats and rabbits show the possibility of destroying or completely transforming the thymus by röntgenotherapy. In his experiments there was found no injury of the organs of the mediastinum. Weil reports 4 cases in which the enlarged thymi were reduced by Röntgen exposures. Weil does not apply large doses, finding the mild amply sufficient. There was no further trouble forty-eight hours after exposure to from 1 to 5 H units with a filter, 18/10. This author's patients were infants between two and one-half and nine months old. As a rule, the number of exposures ranged from 5 to 12. Meyer gave 47 very mild exposures in his case.

H. Klose warns against the use of *x*-rays on children, stating that we do not know the degree of involution of the gland under this influence. Many sittings are necessary, and the rays can injure the child's body in a way that is inestimable. Deficient growth, osteomalacic disturbances, and idiothymica have been observed in children where the thymus was absent. It follows, from these observations, that the thymus must not be totally removed in earliest childhood.

Olivier maintains that operative treatment of the hypertrophied thymus is the only reliable and curative measure that can be applied. Thymectomy is safer and gives better results than röntgenotherapy, resection of the manubrium, or fixation of the thymus to relieve disturbances from it. The organ is easily shelled from its capsule. Attempts to remove the capsule fail. Less than 50 operations have been performed for the removal of the thymus, most of them because of chronic and recurring stridor or dyspnea. Olivier reports 42 thymectomies with 23 cures. The author states that the operation is an excellent one, since it relieved dyspnea in 25 out of 28 cases, the crises of suffocation in 10 out of 12, and the stridor in 12 out of 16. There were 15 deaths in the 42 cases, most of which occurred through sepsis due to the complications of tracheotomy or possibly from difficulties of drainage. Since such complications may occur, it is recommended that the operation of thymectomy, which is not difficult, be made before resorting to prolonged treatment by medication or x-ray. Pedrazzini prefers chondrotomy of the first costal cartilages close to the sternum. He states that this operation is simple, relieves compression, and that it usually has to be done as an emergent intervention. Hotz favors surgical treatment when the symptoms indicate compression of air-passages from an abnormally large thymus. Chevalier Jackson extirpated the thymus, with permanent recovery, after having secured temporary relief by tracheotomy. Hart maintains that tracheotomy is not a good procedure, but that the gland must be partially or totally removed, or space made for it by partial resection of the manubrium. Klose and Vogt reported 8 tracheotomies which were fruitless. Klose performed tracheotomy on a child six years of age, and the patient suffocated in one hour. Rehn states that the success of this procedure is only temporary.

The weight of evidence from scientific investigations and statistical results indicates that, for the treatment of thymic enlargement, medication is at best slow and indefinite, if not absolutely negative, in its effect. Röntgen rays, also, act slowly, often indefinitely, are not sufficiently controllable in their effects, and, according to authorities, the results are not lasting. On the other hand, the effects of operative treatment are practically immediate, the preservation of sufficient thymic tissue for functional need can be assured, neighboring structures are not injured, the procedure is comparatively easy, and the results are good.

OPERATION

Technic.—A curved transverse incision, which includes skin and platysma, is made low in the neck. The inner borders of the attachments of the sternomastoid muscles are incised; the sternohyoids are cut across. If the thymus be enlarged, it is seen as a pinkish gland projecting into the neck from behind the sternum. The gland may now be caught gently with clamps, and drawn upon until the fingers can be used for direct traction. The vessels are not large, the fascia which incloses the gland is loose, and there is but little difficulty in clamping and ligating as one lobe is removed. If it be deemed necessary, the second lobe can be elevated and a portion of it excised. The cure is complete. A drain should not be used unless indications for drainage are urgent. In case it be advisable, a folded strip of rubber tissue should suffice for the few hours during which the procedure may be necessary.

SUMMARY

1. The thymus is an organ of internal secretion, and of essential importance in the vital processes of the body.

2. The combination of epithelial reticulum and lymphocytes indicates that its structure is composed of two parts, which are embryologically, morphologically, and also physiologically different.

3. The life of the gland consists of two phases,—one of progression, the other of regression,—but the old view, namely, that the thymus completely disappears, is now considered erroneous. Remnants of thymic tissue are commonly observed in old age, consequently the expression "persistent thymus" should be dropped. In this relation Hammar favors designating the normal, subnormal, and supranormal parenchymatous value of the gland, which seems a scientific advancement in its description. The stage of physiologic regression probably begins about the time of puberty, but the gland frequently undergoes a pathologic involution, the effect of infectious diseases, inanition, exhaustion, etc. *X*-rays cause a similar result, affecting principally the lymphocytic elements of the organ.

4. Experimental extirpation of the thymus seems to prove that it is an important organ during the period of active growth; that its function is concerned with general development, and particularly with the ossification of bone. Resultant changes are noted in various structures throughout the body in the early period of life. Alterations of the mental state, acid intoxication, and severe cachexia have been observed coexisting with thymic deficiency.

5. Evidence indicates that the secretion of the thymus acts antagonistically to adrenalin. The correlationship of the thymus with the thyroid appears to be coördinative.

6. The mechanic theory of sudden death seems to have been too frequently applied. Whereas thymic pressure may be the causal factor of death in some cases of helpless infants, in strong children and adults it is now practically excluded. In some of the reported cases capillary bronchitis and intestinal disease have been noted in association with the enlarged thymus. Since death has been observed to occur suddenly in these conditions, their causative importance or their presence must be excluded before considering the death thymic. That the enlarged thymus can mechanically cause respiratory and circulatory disturbances seems to be strongly supported by clinical observations plus immediate operative relief. In the presence of such clinical pictures in children the possibility of thymic pressure should always be considered. In cases of sudden death, where the thymus is found enlarged, and respiratory, intestinal, and other serious diseases are excluded, the chromaffin system should be examined for insufficiency. The possibility of status thymicolymphaticus should not be overlooked; the various peculiarities of this condition should be sought.

7. The causal importance of thymic enlargement alone in serious disturbances and death is still a debatable question. Assuming the frequent coexistence of thymic hyperplasia with goiter, which is maintained by several, the statistics of mortality, cure, and relief following operations on the thyroid do not seem to support the significant rôle ascribed by some to simple enlargement of the thymic gland.

8. Recent studies indicate that status thymicus, status thymicolymphaticus, and status lymphaticus are to be separately considered. The anatomic diagnosis of genuine status thymicolymphaticus in very young children is at present impossible—at least, extremely difficult. The lymphatic system of the child is very sensitive to irritations, such as diseases of the intestinal tract, etc. A sharp distinction must be made between lymphatism of

congenital origin and acquired lymphatism. The former presents organic changes, which are closely related to the status hypoplasticus of Bartel and the eunuchoid type of Tandler and Grocz. The acquired form is, in the majority of cases, the effects of previous infections or intoxications. It is also said to result rarely through correlation with other irregularly functionating glands of internal secretion. Despite some clinical reports, the fact remains that our chief knowledge of status lymphaticus is of the changes observed at autopsy. The disease is comparatively rarely diagnosed during life. This emphasizes the need of those doing autopsies constantly to make observations with the object of determining signs available for the clinician. Schridde, in a recent paper, has emphasized this point. This author states that in all of his autopsies where this condition was present there was a hyperplasia of the lingual follicles. He emphasizes this finding both because of its constancy and also because these follicles are rarely inflamed. The signs observed by v. Neusser, which are cited under status thymicolymphaticus in this paper, should be kept in mind.

9. The recent observations which have been made on the association of status thymicolymphaticus with Addison's disease and exophthalmic goiter deserve careful consideration. This seems to be a fertile field for investigation.

10. Operative treatment of the enlarged thymus has given the best results. It is comparatively easy, controllable, and relief is practically immediate. Tracheotomy is usually futile. Drainage should be avoided if possible. Intracapsular thymectomy is the operation of choice.

REFERENCES*

Abelin: "Kinderk. in Stockholm für das Jahr, 1868."
Adami: "Principles of Pathology," Philadelphia, 1908.
Ambrosini: "Thèse de Paris," 1894.
Bang: "Beitr. z. chem. Phys. u. Path.," 1904, pp. 115, 331, 367.
Bordet and Autertin: "Compt. rend. Soc. de biol.," 1909, vol. lxvi, pp. 1101-3.

---

*A complete bibliography of the literature on the thymus may be found in the following articles: Hammar: "Ergebnisse der Anat. und Entwicklung," 1909, vol. xix; Wiesel: "Ergebnisse der pathol. Anat. von Lubarsch u. Ostertag," 1912, 15. Jahrg., Abt. ii.

Bircher: "Schweizerische Rundschau f. Med.," Jahrg. 1910, p. 452.
Bianchi: "Patologica," Anno 3, 1911, p. 223.
Blumenreich: "Berlin. klin. Woch.," 1896; also "Virchow's Arch.," 1900, vol. clx, p. 35; also "Arch. f. path. Anat.," 1900, vol. x, pp. 35–74.
Born: "Arch. f. mikroskop. Anat.," 1882, vol. xxii.
Basch: "Jahrb. f. Kinderh.," 1908, vol. lxviii, pp. 668–691; also "Amer. Jour. Dis. Child.," February, 1912.
Basch and Rohn: "Deut. med. Woch.," 1911, vol. xxxvii, pp. 1843–1848.
Barbano: "Virchow's Arch.," 1912, vol. ccvii, pp. 1–27.
Becker: "Inaug. Diss.," Berlin, 1896.
Bovaird and Nicoll: "Arch. Pediat.," 1906, vol. xxiii, pp. 641–668.
Bednar: "Die Krankheiten der Neugeborenen und Säuglinge," 1852, p. 64.
Bourneville: "Progrès méd.," 1900, vol. xxix, p. 289.
Bonnet: "Lyon méd.," vol. cxii, p. 337.
Beneke: "Berlin. klin. Woch.," 1894, No. 9; also "Münch. med. Woch.," 1909, vol. lvi, p. 1209.
Bartel: "Wien. klin. Woch.," 1910, Jahrg. 23, p. 495.
Bernheim-Karrer: "Korrespondenzbl. f. Schweiz. Ärzte," 1904, Jahrg. 34, p. 53.
Birch-Hirschfeld: "Gerhardt's Handb. d. Kinderkrankh.," 1878, vol. iii, 1. Teil, p. 345.
Bayer: "Ergebnisse d. allgem. Path. u. path. Anat. d. Menschen u. d. Tiere," 1901, 14 Jahrg., 2. Teil.
Bittorf: "Die Pathologie der Nebennieren und der Morbus Addisonii," Jena, 1908.
Birnbaum: "Klinik der Missbildungen und der kongenitalen Erkrankungen des Fetus," Berlin, 1909, p. 91.
Bischoff: "Entwicklungsgeschichte der Säugetiere und des Menschen," Leipzig, 1842.
Collin and Lucien: "Bibliog. anat.," 1906, vol. xv, pp. 24–38; also ref. in. "Zent. f. norm. u. path. Anat.," vol. iii, p. 44.
Capobianco: "Arch. Ital. de. biol.," 1892.
Clessin: "Münch. med. Woch.," 1898, p. 330.
Capelle: "Münch. med. Woch.," September 1, 1908; also "Beit. z. klin. Chir.," 1911, vol. lxxii, pp. 214–238.
Czerny: "Jahrb. f. Kinderheilk.," 1905, p. 199.
Carpenter: "Pediatrics," 1896, vol. ii; also "Proc. Roy. Soc. Med.," 1909–10, vol. iii, pp. 46–48.
Chiari: "Verhandl. d. 66. Versamml. deutsch. Naturf. u. Ärzte," Vienna, 1894, 2. Teil, 2. Hälfte, p. 2, and "Zeitschr. f. Heilk.," 1894, 15.
Clark: "The Lancet," 1896, vol. ii, p. 1077.
Dudgeon: "Brit. Med. Jour.," 1903, vol. ii, pp. 1533–6; "Trans. Path. Soc., London," 1904, vol. lv, pp. 151–203; *ibid.*, 1905, vol. lvi, pp. 1–20, 238–250.
D'Oelsnitz: "Bull. Soc. de pediat. de Par.," 1909, vol. xi, pp. 357–362; also, "Bull. Soc. de Pediat.," 1911, vol. xiii, pp. 304–321.
Daut: "Jahrb. f. Kinderheilk.," 1898, vol. xlvii, p. 141.
Dreschfeld: "Deut. med. Woch.," 1891, Jahrg. 17, p. 1176.
Dubois: "Arch. gén. d. méd.," 1851, 4 ser., p. 223.
Derselbe: "Arch. f. Kinderheilk.," 1900, vol. xxix, p. 344; also "Handb. d. Kinderheilk. von Pfaundler-Schlossmann," 1910, 2. Aufl., 3, p. 448.
Ehrlich: "Encyklopädie die mikroskopischen Technik," 2 Aufl., 1910.
Eberle: "Inaug. Diss.," Zürich, 1894.
Escherich: "Berlin. klin. Woch.," 1896, Jahrg. 33, p. 645.
Friedleben: "Die Physiologie der Thymus," Frankfurt a. M., 1858.
Fortescue-Brickdale: "Lancet," 1905, vol. ii, pp. 1029–1031.
Friedländer: "Arch. of Pediat.," October, 1911, vol. xxviii, pp. 810–829.
Fürth: "Pathologie und Therapie der kongenitalen Syphilis," 1879, p. 62.
Farret: "Thèse de Paris," 1896.
Feer: "Korrespondenzbl. f. Schweiz. Ärzte," 1904, vol. xxxiv, pp. 2, 45.
Fajerstajn: Tübingen, 1902, bei Pietzker.

Fischer: "Inaug. Diss.," Berlin, 1896.

Friedjung: "Zentralbl. f. d. Grenzgeb. d. Med. u. Chir.," 1900, 3, pp. 465, 523, 587; also "Diseases of Children," Pfaundler and Schlossman, 1908, vol. iii, pp. 426–434.

Ganghofner: "Verhandl. d. 74. Versamml. deutsch. Naturf. u. Ärzte," Carlsbad, 1902, 2. Teil, 2. Hälfte, p. 288.

Gebele: "Beitr. z. klin. Chir.," 1910, vol. lxx, pp. 20–86.

Goldflam: "Neurol. Zentralbl.," 1902, p. 154.

Grandhomme: "Inaug. Diss.," Heidelberg, 1900.

Grawitz: "Deut. med. Woch.," 1888, Jahrg. 14, p. 429.

Gluck: "Berl. klin. Woch.," 1894, p. 670.

Griffith: "New York Med. Jour.," 1909, vol. xc, pp. 444–448.

Gierke: "Münch. med. Woch.," April 16, 1907, pp. 775–777.

Garre: "Wien. klin. Woch.," 1911, vol. xxiv, p. 616.

Hasse: "Spez. pathol. Anat.," 1841.

Hart: "Münch. med. Woch.," 1908, Jahrg. 55, pp. 668, 744; also "Virchow's Arch.," vol. ccvii, H. i, pp. 27–55.

Hedinger: "Verhandl. d. med.-pharm. Bezirksvereines Bern, Sitzung vom 10. Mai, 1904," "Korrespondenzbl. f. Schweiz. Ärzte," 1904, Jahrg. 34, p. 606.

Heidenhain: "Berlin. klin. Woch.," 1896, Jahrg. 33, p. 891.

Herz: "Die akute Leukämie," Wien, 1911, bei Deuticke.

Heineke: "Mitt. a. d. Grenzgeb. d. Med. u. Chir.," 1905, p. 21.

Hammar: "Ergebnisse der Anat. und Entwicklung," 1909, vol. xix; also "Wien. med. Woch.," 1909, vol. lix, pp. 2746, 2795, 2910.

His: "Zeitschr. f. wissenschaftl. Zoölog.," 1860, vol. x, p. 333; *ibid.*, 1861, vol, xi, p. 65.

Henle: "Zeitschr. f. rat. Med.," 1849, vol. vii.

Howland: "Arch. of Pediatrics," 1907, vol. xxiv, p. 590.

Hornowski: "Virchow's Arch. f. path. Anat.," 1912, vol. ccviii, H. 3, pp. 414–420.

Hinrichs: "Berlin. klin. Woch.," 1908, Jahrg. 45, pp. 825–828.

Hansemann: "Berl. klin. Woch.," 1905, p. 65.

Hedinger: "Jahrbuch f. Kinderheilkunde," 1906, vol. lxiii, p. 308.

Hotz: "Beitr. z. klin. Chir.," 1907, vol. lv, pp. 509–541; *ibid.*, 1907, vol. lv, pp. 509–541.

Hennig: "Lehrbuch der Krankheiten des Kindes," Leipzig u. Heidelberg, 1859.

Hönnike: "Münch. med. Woch.," 1905, p. 1224.

Jackson: "Jour. Amer. Med. Assoc.," 1907, vol. xlviii, pp. 1753–1756.

Jacobi: "Trans. Assoc. Amer. Phys.," 1888, vol. iii.

Joffray: "Progr. méd.," 1894, vol. xix, pp. 61, 165, 205, 217.

Jonson: "Arch. f. mikrosk. Anat.," 1909, vol. lxxiii, pp. 390–443.

Kutscher: "Zeitschr. f. physiol. Chem.," 1901–2, p. 114.

Kaplan: "Inaug. Diss.," Berlin, 1903.

Kassowitz: "Verhandl. d. 74. Versamml. deutsch. Naturf. u. Ärzte," Carlsbad, 1902, 2. Teil, 2. Hälfte, p. 291.

Koch: "Deut. med. Woch.," 1911, 37. Jahrg., p. 1102.

Kocher: "Mitteil. a. d. Grenzgeb. d. Med. u. Chir.," 1902, vol. ix, p. 1.

Kölliker: "Mik. Anat.," 1852, vol. ii, 2. Hälfte.

König: "Zentralb. f. Chir.," 1897, vol. xxiv, p. 605; also "Verhandl. d. deut. Gesellschaft f. Chir.," 1906, vol. xxxv, p. 69.

Kolisko: "Handb. d. ärztl. Sachverständigen-Tätigkeit," 1906, vol. ii, p. 701.

Kyrle: "Wien. klin. Woch.," 1910, 23. Jahrg., p. 1583.

Klose and Vogt: "Arch. f. klin. Chir.," 1910, vol. xcii, pp. 1125–1141; also "Beitr. z. klin. Chir.," 1910, vol. lxix, pp. 1–200.

Kopp: "Denkwürdigkeiten der ärztlichen Praxis," Frankfurt a. M., 1838.

Kostlivy: "Rev. de Med. technique," 1909, vol. ii, p. 64.

Kaiserling: "Virchow's Arch.," 1902, vol. clxvii, p. 296.

Lasvenes: "Thèse de Paris," 1891.

Lenormant: "Jour. de Chir.," 1909, vol. ii, pp. 601–621; *ibid.*, September, 1912, pp. 273–285.

Lucien and Parisot: "Arch. de. Méd. Exp.," 1910, No. 10, vol. xxii, pp. 98–137.
Letulle: "Arch. gén. d. a. méd.," 1890, vol. clxvi, p. 641.
van Lier: "Beitr. z. klin. Chir.," 1910, p. 201.
Laqueur: "Deut. med. Woch.," 1902, Jahrg. 28, p. 114.
Lejars: "Semaine méd.," 1897, No. 2, p. 55.
Lang: "Ein Beitrag zur Kenntnis der Thymus-tumoren," 1904.
McCardie: "Brit. Med. Jour.," 1908, vol. i, pp. 196–202.
Mölders: "Inaug.-Diss.," Halle, 1901.
Marfan: "Sem. méd.," 1894, p. 259; "Jour. de méd. int.," 1909, vol. xiii, pp. 95–97; "Arch. de méd. d. enf.," 1910, vol. xiii, pp. 801–847.
Moebius: "Nothnagel's spez. Path. u. Therap.," 1896, vol. xxii, Vienna.
Marine and Lenhart: "Arch. Int. Med.," 1909, vol. iv, pp. 253–270.
Mensi: "La pédiatr.," 1903, p. 65.
Meyer: "Verhandl. d. d. path. Ges.," 1908.
Myers: "Arch. of Pediatrics," August, 1908.
Melchior: "Centralbl. f. d. Grenzgebiete der Med. und Chir.," 1912, vol. xv.
Matti: "Mitt. a. d. Grenzgebieten der Med. u. Chir.," 1912, vol. xxiv, H. 4, 5, pp. 665–821; also "Deut. Zeitschr. f. Chir.," 1912, vol. cxvi.
Maximow: "Arch. f. mik. Anat.," 1909, vol. lxxiv; 1912, vol. lxxix; 1912, vol. lxxx.
Mietens: "Jenaische Zeitschr. f. Naturw.," 1908, vol. xliv, pp. 149–192; also *ibid.*, 1910, vol. xlvi.
Mayer: "Münch. med. Woch.," 1908, p. 1906; also *ibid.*, 1910, p. 513.
McGuire and Park: "Arch. Int. Med.," September, 15, 1912, pp. 214–218.
Mettenheimer, von: "Jahrb. f. Kinderheilk," 1898, vol. xlvi, p. 55.
Nathan: "Bull. d. l. soc. ped.," 1909, vol. xi, p. 187.
Nordmann: "Korrespondenzbl. f. Schweiz. Ärzte," 1889, vol. xix, p. 202; also "Arch. f. klin. Chir.," 1910, vol. xcii, pp. 946–973.
Neumann: "Beitr. z. Klinik d. Tuberkulose," 1911, vol. xviii, p. 399.
Neusser: "Aus Kap. der klin. Symptom u. Diag.," 1911, H. 4.
Neusser and Wiesel: "Erkrankungen der Nebennieren," 1910.
Oser: "Wien. med. Presse," 1878, p. 1628.
Oppenheim: "Die myasthenische Paralyse," Berlin, 1901.
Olivier: "Jour. de Chir.," March, 1912, pp. 233–246.
Orgler: "Virchow's Arch.," 1902, vol. clxvii, p. 310.
Pröbsting: "Münch. med. Woch.," 1900, p. 105.
Plater: "Observat. in hominus affectibus plerisque, etc.," 1614, libri tres iii, p. 172.
Prenant: "Compt. rend. soc. d. biol.," Paris, 1893, p. 546.
Petren and Tharling: *Lot. cit.*
Purrucker: "Münch. med. Woch.," 1899, p. 943.
Pfaundler: "Traité des maladies des enfants de Grancher et Comby," vol. iii, p. 256.
Paltauf: "Wien. klin. Woch.," 1889, p. 877; 1890, p. 172.
Popper: "Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Kl.," 1905, vol. cxiv, 3. Abt., pp. 538–546.
Pappenheimer: "Jour. Med. Res.," 1910, vol. xxii, p. 1.
Rendu: "Dict. Dechambre," art., "Goitre exophtalmique," 1893.
Rokitansky: "Handb. der spez. pathol. Anat.," 1842, p. 152.
Rolleston: "Jour. Path. and Bact.," 1897, vol. iv, p. 228.
Rosenberg: "Inaug. Diss.," Göttingen, 1884.
Richter: "Verhandl. d. 74. Versamml. deut. Naturf. u. Ärzte," Carlsbad, 1902, 2. Teil, 2. Hälfte, p. 290.
Ruhräh: London "Lancet," August 29, 1903; also "Jour. Amer. Med. Assoc.," September 19, 1903, p. 752 (Abstr.).
Rubaschow: "Virchow's Arch.," 1911, vol. ccvi, pp. 141–157.
Rabe: "Bull. et mem. soc. anat.," Paris, 1889, vol. xi, p. 833.
Rolleston: "Jour. Path. and Bact.," 1897, vol. iv, p. 228.
Rohn (and Basch): "Deut. med. Woch.," 1911, vol. xxxvii, pp. 1843–1848.

Ronconi: "Patologica," 1909, p. 565, and "Estrato delle memorie della R. accad. d. scienze, lettere ed arti Modena," 9. ser. 3, Appendize, 1909.
Rehn: "Verhandl. d. deutsch. Gesellsch. f. Chir.," 1906, vol. xxxv, pp. 364–391.
Recklinghausen: *Loc. cit.*
Ritchie: "Jour. Path. and Bact.," 1908, vol. xii, p. 140.
Rössle: "Münch. med. Woch.," 1908, p. 377.
Rudberg: "Arch. f. Anat. u. Entwickl.," 1907, pp. 123, 134.
Schäffer: "Progres méd.," 1908, 3. s., vol. xxiv, p. 469.
Scheele: "Zeitschr. f. klin. Med.," 1890, vol. xvii, p. 41.
Schlesinger: "Arch. f. Kinderheilk.," 1899, vol. xxvi, p. 205.
Schmidt: "Korrespondenzbl. f. Schweiz. Ärzte," 1908, vol. xxxviii, p. 20.
Shiota: "Wien. klin. Woch.," 1909, No. 31.
Schraube: "Inaug. Diss.," Munich, 1908.
Schridde: "Zentralbl. f. allg. Path. u. pathol. Anat.," 1908, p. 865; "Münch. med. Woch.," No. 48, November 26, 1912, pp. 2605–2608.
Schwinn: "Jour. Amer. Med. Assoc.," 1908, vol. l, pp. 2059–2061.
Strümpell: *Loc. cit.*
Syk: "Upsala Lakareforenings Forhanlingar," 1909, vol. xiv.
Ssokolow: "Archiv. f. Kinderheilkunde," 1912, vol. lvii, No. 1.
Serrelach and Pares: "C. r. h. se. Soc. Biol.," December 28, 1907.
Stöhr: "Anat. Hefte," 1906, vol. xxxi, pp. 407–457.
Sokoloff: "The Thymus Gland in Man," 1910.
Sury, von: "Vierteljahresschr. f. ger. Med.," 1908, p. 88.
Sappey: "Traité d'anatomie humaine," 1877.
Seiler: "Mitt. a. d. Grenz. d. Med. u. Chir.," 1912, vol. xxiv, pp. 4–5.
Schultz: "Mitt. a. d. Grenz. d. Med. u. Chir.," 1906, vol. xvi.
Sahli and Mettenheimer: "Die topographische Percussion im Kindesalter," 1882.
Svehla: "Arch. f. exper. Pathol. u. Pharm.," 1900, vol. xliii.
Smith: "London Lancet," 1908, vol. ii, p. 1369.
Thorbecke: "Inaug. Diss.," Heidelberg, 1905.
Tandler and Grocz: "Wien. klin. Woch.," 1910, p. 459.
Testut: "Traité d'anatomie humaine," 1894, vol. iii.
Virchow: "Virchow's Arch.," 1853, vol. v.
Vincent: "Proc. Physiol. Soc. Lond.," 1903, vol. xxx, p. xvi.
Vogt (and Klose): "Beitr. z. klin. Chir.," 1910, vol. lxix, pp. 1–200.
Weil: "Lyon. méd.," 1910, No. 47.
Weigert: "Berl. klin. Woch.," 1896, p. 887.
Weidenreich: "Münch. med. Woch.," 1912, No. 48, pp. 2610–2615.
Weissflog: "Inaug.-Diss.," Zürich, 1860.
Waldeyer: "Sitzungsber. d. kgl. prenfs. Akad. zu Berlin," 1890, vol. xxv.
Wharton: "Adenographia," Amsterdam, 1659.
Wiesner: "Verh. d. d. deutschen pathol. Gesellsch.," Leipzig, 1909, pp. 217–219.
Wiesel: "Ergebnisse der pathol. Anat. von Lubarsch u. Ostertag," 15. Jahrg., 2. Abt., 1912, pp. 416–782.
Weichselbaum: *Loc. cit.*
Zesas: "Deut. Zeitschr. f. Chir.," 1910, vol. cv, pp. 125–152.

HEAD, THORAX, SPINAL COLUMN, AND EXTREMITIES

ANALYSIS OF 13,000 CASES FOR ERRORS OF REFRACTION*

GERTRUDE BOOKER GRANGER

From October 1, 1890, to June 1, 1912, 13,000 patients were examined for errors of refraction in connection with the work in the Mayo Clinic, and this paper is an attempt to give a general outline of the methods of examination followed, a classification of the various types, and a synopsis of a few of the especially interesting ones.

It is our invariable practice to use a cycloplegic in examining all patients under thirty-five years of age, and homatropin discs, $\frac{1}{50}$ grain, have been found to be very satisfactory for this purpose. In a few cases, where it was believed the results were not what they should be, atropin 1 per cent. was used, and the same results obtained.

In young children and very nervous patients atropin 1 per cent. was always used for four days. Toxic symptoms were not observed in any case following the use of either cycloplegic.

The examination was divided, and part made on two different days. The history of the case was taken, and the patient carefully questioned in regard to occupation, general health, and nasal trouble, all of which may have a bearing upon the refractive error. The actual examination was then begun. This covered distance vision, muscular balance, ophthalmometer reading, and examination of the fundus by the ophthalmoscope. The refractive error was determined by the trial-lens. When this was done, if the patient was tired or nervous, or if it was late in the day, he was asked to return in the morning for the mydriatic. About one hour after the cycloplegic was applied the patient was ready for examination. The distance vision was taken again, the error of refraction determined by the trial-lens, and the fundus examined by the ophthalmoscope. With children and illiterates we have had to depend almost entirely on ophthalmoscopic and retinoscopic examinations.

---

*Read before the South. Minn. Med. Soc., Albert Lea, August 6, 1912. Reprinted from "Journal-Lancet," May 15, 1913.

The patient was then asked to return, if it were possible for him to do so, after the effects of the cycloplegic had passed off, which would be the next or second day thereafter, and the lens which had been determined upon was placed in the trial-frame and the patient asked to read again from the test-chart. In some cases, usually those with high degrees of hyperopia, it was necessary to continue the mydriatic several days after the patient had begun to wear his glasses, in order to assist the muscles to accommodate themselves to the lenses, since without relieving the accommodation many young people would accommodate to a — lens.

The following case is one of many which demonstrates the reasons for using a cycloplegic:

Mrs. W. J., aged twenty-two years, came to us complaining of a constant headache; could not recognize people across the street; could not read or sew; had been told she was very near-sighted, vision in each eye $\frac{20}{40}$; with -1.50 sph. in both, vision $= \frac{20}{15}$. She had been wearing this myopic correction for two years, and after she was put under atropin, 1 per cent., for four days, her vision was found to be $R = \frac{20}{80} - 1$; $L = \frac{20}{80}$; with spheric 1.25, with 0.25, axis 90, vision $= \frac{20}{15}$ right eye; with spheric $+ 1.50$, with $+0.50$, axis 90, vision $= \frac{20}{15}$ left eye. Glasses prescribed were spheric $+0.25$ with $+0.25$, axis 00, right; and spheric $+0.50$ with $+0.50$, axis 90, left. One year later the patient was able to sew and read; her distance vision was good, but she still had some trouble with her accommodation.

In all cases of headache the differential diagnosis was made of eye-strain or headache from other causes. I believe the eyes are chiefly at fault in the majority of cases.

Many persons with a high degree of refractive error never complain, while others with a low degree, whose general health or nervous condition is not good, will be constantly having trouble, and a high degree of hyperopia and a low degree of myopic astigmatism will give the most trouble, the latter often affecting the general health.

A great many patients come to this clinic after having undergone a serious operation, or having suffered from a severe illness, and complain that their eyes are failing. This is probably due to the fact that, before operation or illness, all their work was done with an effort, though they did not realize it, and that, on account of the general muscular relaxation following the operation or illness, they were unable to regain control of the muscles of accommodation and hence believe their eyes to be weaker than before.

A short time ago a mother brought her little girl to us, saying that the teacher advised an examination of the eyes, as the child had not been doing good work since her illness, although before that time she had been doing excellent work. A high degree of hyperopia was found.

When patients come to us for a change of their glasses, saying their eyes are failing, the ophthalmoscope often reveals one of the following pictures: (*a*) The vision is found to be low, and on ophthalmoscopic examination we may find a few white splashes and a few hemorrhagic spots along the arteries; or (*b*) the splashes may be surrounding the macula, and the arterial walls may be found to be sclerotic. This is diagnostic of albuminuric retinitis. In such cases life is apt to be a matter of months, rather than of years.

Again, we may find a group of shining, punctate dots in the macular region, due to senile changes, for which little or nothing can be done.

Patients having toxic amblyopia usually complain that things look misty or that they cannot read. The ophthalmoscope may show hyperemia of the papilla, or, later in the disease, an atrophic appearance of the temporal side of the nerve-head.

On the other hand, the blurred vision may be due to lues, in which case the ophthalmoscope will show a diffuse exudation or an indistinct disc. These cases are always referred to the laboratory for a Wassermann test.

We have many persons coming to us saying that their eyes have always been weak and are now slowly failing. Very often they give a history of other members of the family also having weak eyes. We find retinitis pigmentosa which is slowly progressive, but in which there is usually enough sight preserved for the patient to get about. In all the cases which I have seen none has been totally blind.

In the examination of a patient for a change in his lens we frequently find an Argyll-Robertson pupil, that early symptom of tabes, but with the eyes normal in every other respect. These patients are invariably referred for a general examination.

We must also consider the nose in its relation to the eye, and every nasal abnormality should be taken into account as a possible cause of headache. Very often the first intimation of sinus trouble is indicated by symptoms referred to the eyes. When this occurs in a case which has a corrected error of refraction, the patient's first thought is that his lenses should be changed. Hence the oculist must understand the relation between the nose and the eye, and be prepared to treat nasal disease if his patients are to obtain the relief they seek and expect, or else he must refer his patient to a rhinologist.

In view of the fact that in a very large percentage of cases of migraine a general examination and an examination of the nose and eyes will not reveal any cause, I have reached the conclusion that, in a great majority of cases, it must be called hereditary. This conclusion is greatly strengthened by the fact that in most of these cases a history of migraine can be traced back through several generations.

A Series of Congenital Cataracts

In September, 1910, Mr. B. R. brought four children to us: Carrie, aged twelve; Dennis, aged nine; Mary, aged seven; and Nettie, aged six. Each had congenital cataracts, and on taking their histories it was found that the mother had cataracts removed when a child, and it was thought prenatal worry was the cause of the cataracts in the children, as the trouble was noticed when they were babes. All of them had been operated on before coming to us. Carrie, with correction, vision $=\frac{20}{20}$, and Dennis had convergent alternating squint. It was found necessary to perform another operation upon each of the three youngest, after which glasses were given and the children could see to get about and could distinguish objects around the room. All the children had been in a school for the blind, depended on their sense of touch, and had yet to learn the use of their eyes.

J. P., aged twelve years, was brought to us with congenital cataracts. His mother noticed at three months of age that the babe had some trouble with the eyes. He had one brother and one sister with the same trouble, but I could not get a history of cataracts on either the father's or the mother's side.

Mrs. C. H., aged thirty-eight, gave a history of eyes never having been good, but did not think that the vision had decreased in the last few years. On examination, small congenital cataracts were found in the center of each lens, with vision to either side about $\frac{1}{3}$. Her mother and grandmother had each had the same trouble.

January, 1907, Mrs. A. aged forty-three, came complaining of severe pain in the left eye. Upon examination her vision was found to be merely a perception of light. The tension was +, and the media were full of floating specks. Glaucoma was diagnosed, an iridectomy advised, and an operation was performed the next morning. The eye became quiet after the operation, but there was no improvement in the vision, which had been low since the right eye had been injured and enucleated sixteen years before.

June 4, 1907, Will, aged fifteen, son of patient Mrs. A., was brought to us. His left eye had been enucleated when a small child; he gave a history of a blind eye which had become protruding and painful and therefore had been removed. The sight of the right eye was never good, and for six years had been blind; he had been told he had congenital cataract and wanted it removed; the lens was found to be opaque and calcareous; the eyeball was shrunken; there was only perception of light, and it being apparent that no beneficial results would follow, an operation was not advised.

June 4, 1907, another son of Mrs. A., Paul H., aged thirteen, who had always been very near-sighted, was examined. In December, 1906, he had accidentally discovered that he could not see with his left eye. On examination a detached retina was found, and the vision in right eye was $\frac{5}{200}$, with a correction of sph. -6, -1.50, axis 180, vision $=\frac{20}{60}-1$. Last December (1911) the boy was returned to us with left eye inflamed and very irritable, the lens opaque, tension+, and glaucoma was diagnosed. Evisceration was advised, and an operation performed. Vision in right eye is now $\frac{20}{40}$ with correction.

May 13, 1908, he was followed by another member of the family, Ellis, aged seven, who had a high degree of myopia with nystagmus, vision $\frac{20}{200}$, sph. -7 lens, vision $=\frac{20}{80}-$. He was given this correction in both eyes. In April, 1909, upon another examination, it was found that the vision remained the same. In July, 1909, he returned with the vision gone in the right eye, and a detached retina was found. Vision in the left eye is now (1912) slowly failing, and the child is with his brothers in the school for the blind.

In December, 1911, Allen, aged four, the youngest and last member of the same family, was brought to us. The parents thought his eyes were good until a year ago. They then made a test of each eye separately, and found the left eye to be blind. He had detached retina and the right eye was very myopic. The father of the family and one son have normal vision. One child had died, at the age of six months, with convulsions.

In some patients with high myopia, K. I. has been found very beneficial. After using it for six weeks or two months the vitreous is clearer and vision improved.

The cases examined have given the following results, which it is believed will prove to be general averages:

Presbyopia (17.5 per cent.)	2279
Hyperopia (12.4 per cent.)	1615
Hyperopic astigmatism (13.1 per cent.)	1708
Compound hyperopic astigmatism (9.1 per cent.)	1250
Myopia (6.2 per cent.)	815
Myopic astigmatism (6.8 per cent.)	895
Compound myopic astigmatism (5.7 per cent.)	751
Mixed astigmatism (2.3 per cent.)	305
Myopic in one eye and hyperopic in the other (0.5 per cent.)	185
Cataracts (4.1 per cent.)	572
Exophoria (4.3 per cent.)	562
Esophoria (4.2 per cent.)	555

In 2625 cases (20.2 per cent.) no glasses were prescribed, although every symptom of eye-strain was mentioned by the patient. In the majority of these cases a mydriatic was used, and nothing being found to account for the symptoms complained of, the cases were returned to the family physician for general treatment.

THE RELATION OF NASAL CONDITIONS TO ANAPHYLAXIS AND ASTHMA*

JUSTUS MATTHEWS

Asthma is a condition or symptom-complex characterized by intermittent paroxysmal dyspnea and vasosecretory disturbances. As yet, so little is positively known of its etiology and pathology that great differences of opinion exist as regards an exact definition of the affection.

So-called cardiac and renal asthma are not considered in this discussion, since they are not true asthma but rather dyspnea, and are clearly distinguishable from asthma proper.

The principal pathologic conditions exhibited by an attack are spasm of the bronchial and other respiratory muscles, especially the diaphragm, and turgescence, edema, and hypersecretion of the mucous membranes of the respiratory tract, resulting in extreme emphysema of the alveoli.

Of the 200 cases diagnosed as "asthma" in the Mayo Clinic during the past three years, in sixteen there were lesions of the heart, lungs, or kidney sufficient to give symptoms overshadowing those from all other sources. Some of the patients also had pathologic conditions in the upper respiratory tract of secondary importance, which may have contributed to the symptoms.

In 184 of the series the principal lesions were found in the nose, in the accessory nasal sinuses, or in the nasopharynx. One hundred and fifty-seven of these had evident purulent, mucopurulent, or seropurulent discharge in the nostrils or in the nasopharynx.

---

* Read in the Section on Laryngology, Otology, and Rhinology of the American Medical Association, at the Sixty-third Annual Session, held at Atlantic City, June, 1912. Reprinted from the "Jour. Amer. Med. Assoc.," September 21, 1912, vol. lix, pp. 1107, 1108.

Fifty-eight had polypi in one or both nostrils, 52 had polypoid degeneration of the mucous membranes of the middle turbinals, and 1 of the ethmoid region.

Sixty-three patients had suppuration of one or both antra, and 19 antra which produced no pus on irrigation were dark on transillumination. In some of these cases there was undoubtedly an inflammatory condition of the antrum without the accumulation of pus.

Twelve children, from eleven months to eleven years of age, had large tonsils and adenoids, associated with, and probably in most cases the cause of, chronic edematous rhinitis. Of the 200 patients under observation, 138 have been treated by operation, local applications in the nostrils, or by irrigation of the accessory sinuses.

Reports from 104 patients, treated more than six months ago, have been received and are tabulated below as to results, without regard to the extent to which the treatment had been carried.

RESULTS, AFTER SIX MONTHS, OF THE TREATMENT OF 104 PATIENTS

	Entirely Relieved	Markedly Improved	Slightly Improved	Not Improved	Total Number
Local applications or irrigations of the accessory sinuses	8	11	3	4	26
Operations on polypi, middle turbinals, or ethmoid	11	11	13	15	50
Operations on the antra, one or both	5	5	1	0	11
Operations on antra and middle turbinals and ethmoid	2	4	2	1	9
Operations on inferior turbinals or septum	0	1	0	1	2
Operations on tonsils and adenoids	5	0	0	1	6
Totals	31	32	19	22	104

In several instances only a single treatment had been given, or an operation had been performed and its object not assured for want of after-care. Other patients who were free from symptoms for from six months to one year had suffered recurrences and are here classed according to their present condition. Most of these patients are non-residents, and many are in such circumstances that they are unable to remain or to return for satisfactory treatment.

Although the tabulation does not show it accurately, a study of each individual history indicates that, almost invariably, relief of the asthmatic symptoms corresponds in degree to the extent to which the pathologic conditions in the nostrils, nasal sinuses, and nasopharynx have been improved. This response of the more general symptoms of asthma to strictly local treatment in the upper respiratory tract confirms the opinion which the constant association of lesion in that region with asthma has given, viz., that these lesions are the cause of abnormal systemic condition and that asthma is the manifestation of that condition.

Since the publication of the results of experiments in anaphylaxis by Theobald Smith, Otto,[1] Rosenau and Anderson,[2] and others, the theory that in anaphylaxis is to be found the explanation of the occurrence of asthma has been advanced by Meltzer[3] and others. Auer and Lewis[4] have demonstrated conclusively that the dyspnea which is the chief manifestation of anaphylactic shock is produced by stenosis of the bronchioles, by spasm of the circular bronchial muscles, and that, while this stenosis is associated with, it is not dependent on, spasm of the diaphragm, since it can be produced separately. This muscular spasm and the resulting emphysema can be produced in the absence of the central nervous system, thus proving that it is not a reflex but a local reaction to systemic condition.

Exactly the same condition of the lungs exists during a paroxysm of bronchial asthma, and thus it is reasonable to assume that in asthma also the reaction is due to the effect of a general condition on the muscles or nerve-endings of the bronchioles, and that a reflex neurosis is of a secondary importance and not essential to the production of the symptoms of asthma.

It has been proved experimentally for hay-fever and the asthma that accompanies it that, on the introduction of a minute quantity of the toxalbumin of the pollen into the blood of an individual subject to those affections, the symptoms of hay-fever and asthma appear, while in the normal individual no reaction occurs. The same has been found to be true of the emanations of animals in the cases of those sensitive to them. The sensitization has undoubtedly taken place by previous entrance of a foreign proteid into the blood or by heredity, which is an active factor in both asthma and anaphylaxis.

More numerous and more serious are the cases which require the presence of no external irritant to produce the symptoms of asthma, but in which also the symptoms are exactly similar to the anaphylactic reaction. So it is reasonable to assume that in the cases considered as idiopathic asthma there occurs the entrance of a foreign proteid into the blood in some way not yet demonstrated.

It has been found that a foreign proteid capable of sensitizing the individual and later of producing the anaphylactic shock may result from autolysis of retained placenta or other tissues. The frequency with which retained and altered mucoid and purulent discharges are found in the nostrils or nasal sinuses suggests that here is the site of the production and entrance into the blood of the foreign proteid which produces the anaphylactic reaction in these cases. The quantity of the foreign proteid necessary to sensitize and later to produce the anaphylactic reaction in a susceptible individual is so small that the known absorptive powers of the nasal mucous membrane could undoubtedly pass it into the blood under suitable conditions. Moreover, the reaction has been produced experimentally in guinea-pigs by the inhalation of animal emanations followed by the injection of serum from animals of the same species.

The results of treatment of nasal conditions in asthmatic patients present still other analogies to anaphylaxis. Operation to establish free drainage and aëration of the mucous membrane of the nose and accessory sinuses prevents retention of secretion, while in other cases the same may be accomplished by local treatment to stimulate profuse discharge so that secretions are washed away before autolysis occurs. This prevents the formation and intermittent absorption of the specific foreign proteid which causes the anaphylactic reaction, commonly known clinically as asthma.

So long as secretion and drainage are free and continuous, relief from asthma will be complete, but recurrence will usually result from the interruption of drainage even after long periods of immunity from symptoms.

REFERENCES

1. Otto: "Handbuch der path. Mikroörganismen," 1908, vol. ii, p. 255.
2. Rosenau and Anderson: "Arch. Int. Med.," 1909, vol. iii, p. 518.
3. Meltzer: "Jour. Amer. Med. Assoc.," September 17, 1910, p. 1021.
4. Auer and Lewis: "Jour. Exper. Med.," 1910, vol. xii, p. 151.

THE DIAGNOSTIC SIGNIFICANCE OF THE PARAVERTEBRAL TRIANGLE OF PERCUSSION DULNESS* (GROCCO'S SIGN)

FRANK SMITHIES

Within the past two decads very little has been contributed to the physical diagnosis of intrathoracic disease. With the possible exception of Da Costa's work[1] on the percussion of the spine, the "muscle resistance sign," described by Pottenger,[2] and the brief communication of Cabot,[3] calling attention to certain minor auscultatory differences between the two sides of the normal thorax, the only diagnostic procedure of worth in this field has been the clinical observation of the percussion findings, in health and disease, of the posterior thoraco-abdominal boundary. Of these percussion findings, the consideration of the so-called "paravertebral triangle of dulness," emphasized by Grocco, takes first rank. It is somewhat curious that with scores of eminent diagnosticians at work, only desultory mention of this phenomenon should have been made until recently. One can, perhaps, find explanation of this oversight in the fact that careful scrutiny of the posterior thorax is very frequently neglected in both hospital and private practice.

DEFINITION

Grocco's description of the paravertebral triangle of dulness has become classic. In his original communication[4] (March, 1902) he said:

"In a pleural effusion of sufficient size, when percussion is performed from above downward along the vertebral spines, the patient being in a sitting posture, there can be made out, at the level of the effusion, a relative dulness, associated with increasing sense of resistance. As one percusses downward, this relative dulness becomes absolute. Similarly, if one percusses downward on the fluid-free side, in lines parallel to the vertebral spines, *an area of impaired resonance, of a triangular outline, is noted on the side free from effusion.* The boundaries of this area of impaired resonance are, *mesially,* the line of the vertebral spines; *inferiorly,* the lower border of thoracic resonance on the sound side, and at the *outer side,* a line connecting the base-line with the beginning of the superior limit of spinal dulness."

---

* Reprinted from "The Archives of Diagnosis," New York, April, 1912.

Grocco advanced the suggestion that this triangular area of dulness along the spine on the healthy side was of considerable diagnostic worth in the differentiation between pleural exudate and pulmonary consolidation.

HISTORIC DATA

In abnormalities of the lungs and pleura observations of altered resonance in percussion on the side of the thorax apparently healthy are not original with Grocco. In 1878 Rauchfuss[5] observed that dulness to the left of the median line was not uncommon in children affected with right-sided pleural exudate. Similarly, somewhat later, Weil[6] noted that effusion in the right pleural sac, when marked, were associated with a wide area of percussion dulness in the second intercostal space to the left of the sternum. In 1897 von Korànyi,[7] of Budapest, called attention to the fact that in pleural effusions displacement of the posterior mediastinal tissues impaired the resonance of the lower thoracic vertebræ, and gave rise to a somewhat triangular area of dulness extending from the spine outwardly on the sound side. It remained for Grocco,[8] however, to emphasize the observation that in pleural effusions, when fluid encroached upon the spine, this paravertebral triangular area of percussion dulness, when searched for, was an almost constant physical finding. The month following Grocco's first communication, von Korànyi demonstrated, by means of an outline sketch, that with his method of auscultatory percussion he had been able to determine in a case of left-sided pleural exudate a distinct triangular area of dulness on the healthy side. It would seem that while Grocco's name has been intimately associated with the paravertebral triangle of dulness, due credit must be given to Rauchfuss and von Korànyi for early cognizance of the phenomenon.

Since 1902 the literature relating to the above sign has rapidly grown. In Italy, the further communications of Grocco, the confirmatory observations of Flora,[9] F. Maragliano,[10] G. Pierracini,[11] Bucco,[12] Baduel and Siciliano,[13] Padoa,[14] Cecchini,[15] P. Pennato,[16] Siciliano,[17] Banti,[18] Silvestri[19] and Ferrannini;[20] in England, the writings of Ewart,[21, 22, 23] Forbes-Ross,[24] Morison,[25] and Smith[26]; in Germany, the reports of Rauchfuss,[27] Weitz,[28] Jamburger,[29] and Goldscheider;[30] in Latin America the observations of Aroaz,[31] Pruneda,[32] Landa,[33] and de Barros;[34] in France, the papers of Roch and Dufour,[35] Cassaet,[36] and of Brudzinski;[37] and in America, the complete and pioneer work of Thayer and Fabyan[38] and the clinical observations of Frankenheimer,[39] Reilly,[40] Blumer,[41] Gordinier,[42] Beall,[43] Calvert,[44] and Smithies,[45–48] have established the constancy of the presence of transspinal dulness in instances where free fluid is present in a pleural sac. As is to be expected, adverse comments are not lacking. Barbieri[49] and Ghelfi[50] conclude (from an apparently limited experience with the sign) that the paravertebral triangle of dulness has little constant clinical value. Signorelli[51] lays especial emphasis on the importance of spinal percussion, and maintains that absolute dulness or "flatness" is especially pathognomonic of pleural effusion.

More careful study of the posterior, thoraco-abdominal boundary has revealed new facts with respect to the outline of this boundary in both health and disease. It would seem that in health, the lower lung border, posteriorly, is a somewhat flattened arch, with its convexity upwards. As a consequence, unilateral percussion will reveal on each side of the spine a roughly triangular dulness. This is somewhat more marked on the left side when carefully mapped out in subjects with relatively thin parietes.*

---

* This fact has recently received further attention at the hands of Grocco[53] and Ferrannini.[54]

In extrathoracic disease, it was early shown by Ewart that subphrenic abscess or ascites could produce paravertebral dulnesses. These dulnesses were not, however, so characteristically triangular as were those described by numerous observers in cases of pleural effusion. In cases of ascites Ewart some time ago pointed out that these showed triangular dulnesses on both sides of the thoracic spines; that these dulnesses were roughly equal in extent; that they were broad based, but that, in the sense of the dulnesses in cases of pleural effusion, they were not "movable." Beall has reported the presence of definite paravertebral dulness in a case of subphrenic abscess. Gordinier has demonstrated that abscess of the liver may be associated with paravertebral dulness grossly triangular. The writer has called attention to the presence of a similar dulness in the case of abdominal, multilocular cystadenoma, and, followed later by Landa, demonstrated that a left-sided, triangular dull area may be percussed along the spine in the advanced stages of pregnancy.

For the purpose of clearer demonstration of the above conditions the outline charts presented herewith may be consulted.

THEORIES AS TO THE MODE OF PRODUCTION OF GROCCO'S PARAVERTEBRAL TRIANGLE OF DULNESS

In his second communication Grocco demonstrated, by means of radiograms from a case of artificially produced pleural effusion, that there was an opacity crossing over the spine from the affected side to the sound side. He endeavored to show that this opacity (pleural sac?) was sufficient to account for the dulness along the thoracic spines on the fluid-free side. Later, Baduel and Siciliano slowly filled the pleural sacs of a sitting subject with gelatin, after having similarly filled the abdomen (to fix the diaphragm) and injected the carotid. Transverse sections of the thorax were then made. In the case in which the right pleural sac had been filled, the aorta, the esophagus, the azygos vein, and the soft tissues of the mediastinum were noticeably displaced to the left of the spine by the extension of the right pleural sac. Outlines of the section show that the pleural sac itself extends well

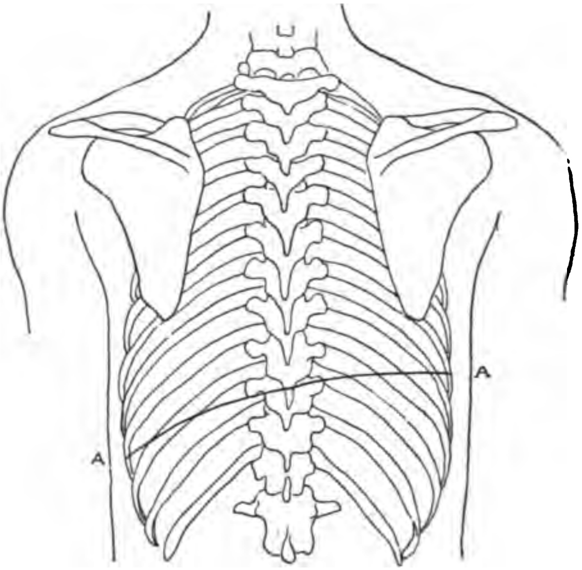


Fig. 198.—A, A, Normal posterior thoraco-abdominal boundary.

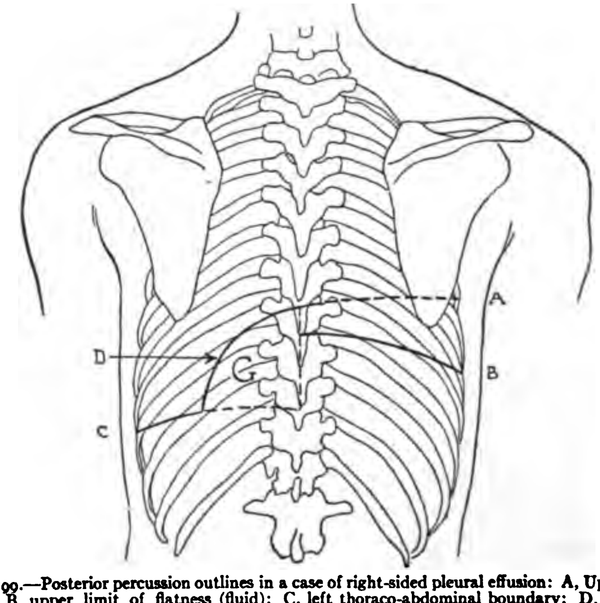


Fig. 199.—Posterior percussion outlines in a case of right-sided pleural effusion: A, Upper limit of dulness; B, upper limit of flatness (fluid); C, left thoraco-abdominal boundary; D, outer limit of paravertebral dulness, left of spine. G, Grocco's triangle.

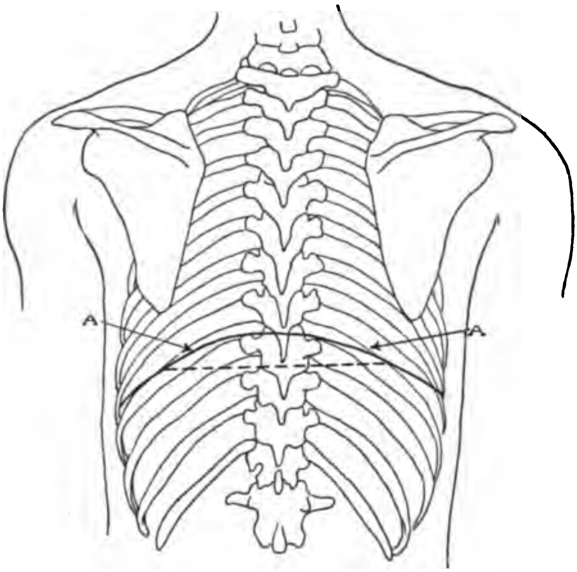


Fig. 200.—Posterior thoraco-abdominal boundaries in a case of ascites. A and A', Triangular dull areas that may be determined on each side of the spine.

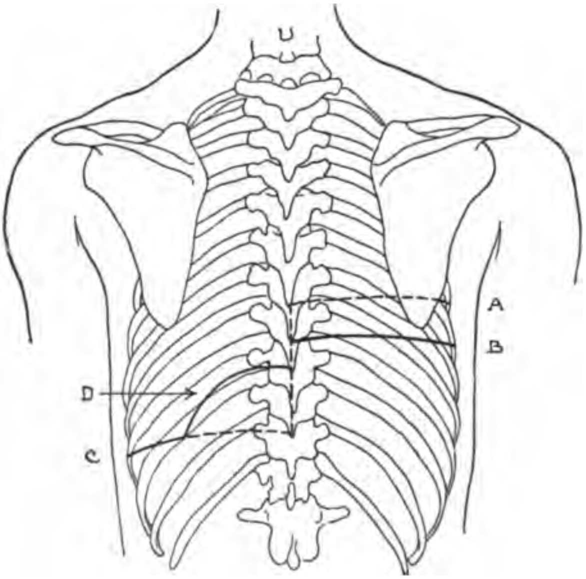


Fig. 201.—The thoraco-abdominal boundaries, posteriorly in a case of abscess of the liver. A, Dulness—compressed air-containing tissue; B, flatness—enlarged liver; C, left thoraco-abdominal boundary; D, atypical paravertebral dulness to left of spine.

across the median line. When the left pleural sac was filled with gelatin, there was displacement of the mediastinal tissues to the right of the spine. The displacement in this experiment did not seem to be so marked as when the right thorax had been injected. Evidences of the increased pressure on the sound side were shown by the fact that when some of the ribs were resected on that side, there was a hernia-like protrusion of the lung. Through the opening made by the resection of the ribs, it was stated that the displacement of the mediastinal structures could be well made out. Rauchfuss radiographed the thorax of a young girl affected with marked right-sided pleural effusion, after having injected a bismuth suspension into the esophagus. Noticeable displacement of the esophagus to the left of the median line was demonstrated, the displacement being greater, apparently, than that existing in the normal, as shown by the experiments of Calvert. Smith exhibits a sketch of the findings in an adult Egyptian peasant,

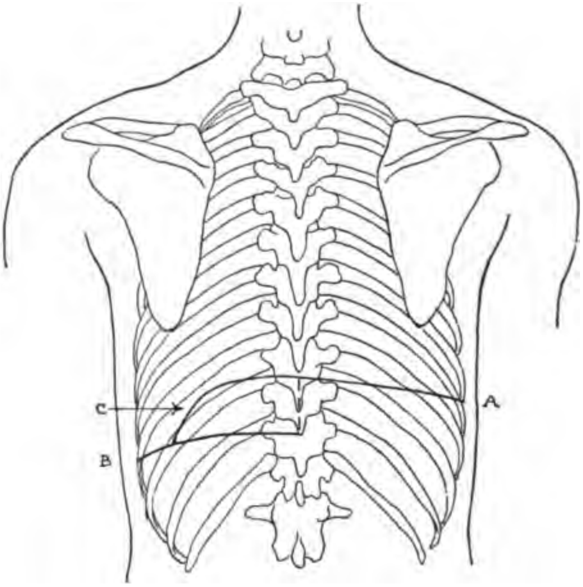


Fig. 202.—Paravertebral dulness in cases of abdominal tumor, *i. e.*, large cysts, advanced pregnancy: A. Upper limit of liver dulness; B, left posterior thoraco-abdominal boundary; C, atypical paravertebral dulness to left of spine.

who was brought, moribund, with marked pleural exudate, into the Kasr-el-Ainy Hospital at Cairo. The body was filled with 10 per cent. formalin solution, given intravenously. The tissues were thus hardened *in situ*, while the fluid in the pleural sac was coagulated in its existing relations to adjacent parts. Sections of the thorax were then made. The heart and the thoracic viscera were shown to be distinctly displaced across the median line.

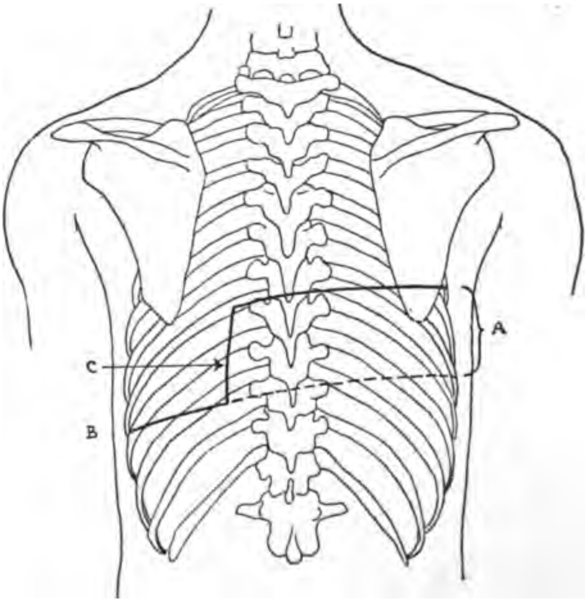


Fig. 203.—Type of paravertebral dulness in massive pulmonary consolidation: A, Airless tissue (consolidated lung); B, lower lung border on left side; C, roughly rectangular dulness along spine to the left, *i. e.*, on the side *not* exhibiting pulmonary consolidation.

When the outlines of the displaced parts were projected upon the thoracic wall, posteriorly, a definite area of triangular shape was demonstrated. It would seem, consequently, from the above cited experiments, that one not negligible factor contributing to transspinal dulness, in cases of pleural effusion, is the mechanic displacement of the thoracic viscera, particularly of the mediastinal structures lying along the vertebral column. This, however, does not seem to be the only factor contributing to the paravertebral dulness. It would also seem that in pleural effusions *which impinge on the spinal column* the air-containing, resonant lung tissue is mechanically separated from contact with the vertebræ. As a consequence, the normal vibrations (or resonance) existing over the spine are inhibited by the close contact with non-resonant fluid. This fluid "acts as a mute" (Baduel and Siciliano). It is probable that this inhibition of the vertebral resonance extends for a variable distance on the opposite side, along the transverse processes of the vertebræ. It would likewise seem that where the accumulation of fluid was greater, *e. g.*, at the lower limit of the pleural sac, there would be more massive "deadening" outward along the transverse vertebral processes. At the upper part of the thorax, where the pleural effusion is usually less in bulk, the consequent "deadening" of the spine's vibration would be less. It is thus suggested that, as a result, the transspinal dulness is less extensive, *i.e.*, there is less outward inhibition to vibration along the transverse processes, and there is less pronounced dulness along the spines of the vertebræ themselves. It would appear that this "tapering off" of the dulness, superiorly, had a certain bearing upon the determination of the shape of the paravertebral dulness on the healthy side. Just what effect pulmonary collapse, spinal musculature, and the contour of the thoracic floor (diaphragmatic) have on the shape of the paravertebral area of dulness still remains the subject of discussion. It would seem reasonable, therefore, to ascribe the transspinal dulness to the concurrence of many factors, with respect to both shape and extent. Each relative variation of such factors correspondingly varies the resulting percussion picture. The anatomic investigations of Forbes-Ross and the comments of Ewart would appear to warrant further experimentation along the lines suggested by those workers.

METHOD OF DETERMINING THE PARAVERTEBRAL TRIANGLE OF DULNESS

The technic has been frequently described. It should be stated that a certain amount of initial skill and of experience with the sign, in relation to the peculiarities of the posterior thorax, are essential for successful or dependable work. It is advisable to have the subject standing or sitting erect, leaning slightly forward. The strength of the percussion stroke must be adapted to the character of the patient's parietes. In very obese or muscular individuals, strong percussion must be performed, else the triangle will either be missed or but poorly delimited.

The limits of the suspected effusion should be first carefully outlined with a wax pencil. The vertebral spines may then be percussed from above downward. A rather strong, firm stroke is indicated. The upper limit of diminished resonance on the spine should be accurately marked. It usually coincides closely with the upper, mesial limit of the effusion. Percussion of the sound side, from above downward and parallel with the line of the spinous processes, should be next performed. It will be seen, in a favorable subject, that as one progresses downward the resonance diminishes on the fluid-free side. Points placed at the diminution of resonance will, when connected with the wax pencil, give a generally triangular area along the spine. The base of the triangle is, in the ordinary case of pleural exudate, the lower limit of thoracic resonance on the sound side. Percussion inward from the axilla of the fluid-free side will frequently be of service in delimiting the lower boundary of the triangle.

Physical Characteristics of the Paravertebral Triangle

The *extent of the triangle* varies to a certain degree with the amount of free fluid in contact with the spine. In general, it may be said that the extent of the paravertebral dulness is directly proportionate to the quantity of fluid on the opposite side of the spine. There are many modifications to this statement. It does not seem, from personal observation of the sign, or from the perusal of the work of others, that the base of the triangle varies so much in breadth according to the quantity of free exudate as does the height. The length of the base is rarely more than seven centimeters. Perhaps this is so because the transverse processes of the vertebræ vary comparatively little in size in the thoracic section of the spine. The corresponding dulness from the presence of fluid on the opposite side would thus seem to depend more on the fact that air-containing tissue has been displaced from contact with the vertebral column than upon the actual amount of fluid causing this displacement. The triangle is usually better mapped out after the subject has been sitting or standing for several minutes than when searched for immediately. The character of the effused fluid appears to have its effect upon the size of the triangle. In cases of hydrothorax, or simple effusion, the triangle is larger and more readily delimited and reveals more marked changes in extent on movement of the patient than when a thick exudate or pus is present. The subject's lying on the affected side usually results in the total disappearance of the paravertebral dulness or in its marked diminution in extent. If the patient lie or lean toward the non-affected side, it is frequently possible better to map out the triangle, and in some cases this procedure will cause the paravertebral area of dulness to appear where the upright position did not make its recognition possible. Ewart and others have made use of these variations in the extent and the form of the transspinal dulness on change in position to distinguish between paravertebral dulness due to effusion, solid thoracic tumor, or pulmonary consolidation. This manœuver is called by Ewart "the crucial test and counter-test." It is of much importance.

Few observers give definite figures respecting the actual extent of the triangle of Grocco. The figures of Thayer and Fabyan are instructive. In 31 cases measured by these writers the base-line of the triangle ranged from 3 to 7 cm. There are no definite figures given for height. This seems to vary with the extent of the effusion, as has been suggested. It would seem that the triangle is more extensive in cases exhibiting right-sided effusion than where the exudate is present on the left side. This does not always hold. In 8 cases of right-sided effusion observed by the author the average length of the base-line was 5.75 cm. The individual measurements ranged from about 3 to 6 cm. In 6 left-sided effusions the length of the base-line averaged 4.68 cm., with individual measurements of from 2 to 7 cm. In one of these cases, in which the base of the triangle measured but 2 cm., more than 500 c.c. of pus were removed at the thoracotomy. This was a case of pulmonary abscess following a lobar pneumonia, where the empyema occurred late. No definite measurements of the height of the paravertebral triangle were possible in the cases where base measurements have been cited. It would seem that in some muscular or obese subjects the line of the effusion dulness may be somewhat lower than the beginning of the diminished resonance on the spine. In the examination of 27 cases the upper limit of the paravertebral dulness was slightly higher in right-sided effusions than in left. The high position of the diaphragm on the right side, due to the encroachment of the liver on the thoracic space, may account for this variation. Aspiration appeared to affect the height of the triangle more than its breadth, particularly where the effusion was serous.

The *form* of the transspinal area of dulness depends on several factors. Care in percussion of the average subject with typical pleural exudate usually reveals a triangle with a somewhat outwardly convex hypotenuse. Percussion with a very strong stroke may modify this, so that the hypotenuse will appear as a straight line or one outwardly concave. The anatomic structure of the subject's back obviously plays an important part in determining details of form of the triangle. The presence of a pulmonic consolidation, an enlarged heart (Ferrannini and others), a double exudate, or an encapsulated effusion may each vary both the size and the shape of the "triangle."

The *dulness* over the paravertebral area is usually a relative one, and can readily be distinguished from the flatness over the spine (where fluid has displaced air-containing tissue) and over the pleural exudate. It is this fact of having a relative dulness that makes the recognition of the transspinal area difficult when the subject is not a favorable one or when the examiner is not familiar with the normal percussion of the posterior thorax. The dulness is generally more definite as one approaches the median line.

Auscultatory phenomena over the paravertebral area are usually not lacking in favorable cases. Plessi,[52] Rauchfuss, Thayer and Fabyan, and others have noted diminished or absent breath-sounds over the triangle's limits. Occasionally there may be broncho-vesicular breathing, tubular respiration, or the presence of fine râles. Bronchophony, egophony, and the so-called "coin-sound" have been reported by some observers. We have never been able to elicit the coin-sound in our cases, even when the effusions have been extensive. The auscultatory phenomena may be entirely lacking, even in effusions of large amount. In one of our recent cases there was absent breathing, without spoken voice alterations, in which more than 500 c.c. of fluid were siphoned from the right pleural sac. In this case a solid tumor was demonstrated in the thorax. The spoken-voice changes are generally more marked after the patient has been upright for a few minutes.

Palpation.—In none of the author's cases could the absence of tactile fremitus be observed over the paravertebral area of dulness, even where there was marked effusion on the opposite side, with a total absence of vocal fremitus. The increased sense of resistance on percussion has already been mentioned.

Position of the Paravertebral Triangle in the Thorax.—As usually described, the base of the triangle coincides with the lower limit of thoracic resonance on the fluid-free side. This is not always the case. In encapsulated exudates and in lung abscesses which finally result in localized empyemas adjacent to the spine, an area of dulness may appear anywhere along the course of the spine on the non-affected side. This area may be rather ovoid than triangular. It rarely lies along the spine as a rectangular area of deficient resonance, as in a frank pneumonia.

CONSTANCY OF THE PARAVERTEBRAL TRIANGLE OF DULNESS IN CASES IN WHICH FLUID MAY BE DEMONSTRATED IN THE PLEURAL SACS

A rapidly increasing literature corroborates the early observations of Rauchfuss, Grocco, and von Korànyi that where free fluid exists in the pleural sac, paravertebral areas of dulness may be percussed on the fluid-free side. In 32 cases Thayer and Fabyan demonstrated the transspinal dulness in 30. Frankenheimer noted its constant presence in 31 cases. From a large experience, Ewart claims that it is always possible to demonstrate the paravertebral dulness when the effusion is extensive enough to impinge on the spinal column. Ewart also maintains that the sign is of extreme importance when the amount of effusion is less than one-fifth of the capacity of the pleural sac affected. When the transspinal dulness disappears or is markedly altered on change of position of the patient, it would appear that the sign is absolutely pathognomonic for free fluid in the pleural cavity. This test, as has been mentioned, is laid emphasis upon by Ewart. Of 27 cases of pleural effusion, Gordinier found the transspinal dulness constantly present. In 42 cases of pleural exudate we have been able to demonstrate the paravertebral dulness in 39. In three cases where the sign was not determined there were, respectively, encapsulated effusion, not reaching the spine, a case with marked obesity with acute pleurisy, and an interlobar empyema.

In double effusions, Ewart has called attention to the fact that two paravertebral triangles may be percussed, and that after puncture, alterations in the extent of the triangles can readily be demonstrated. In 2 cases of double effusion we were able to demonstrate only one typical Grocco's triangle in each case before aspiration. It was in each case on the side with the less effusion. After tapping, the cases showed a transference of the triangles from one side to the other, according to the predominance of the exudate. It is true that when double effusions exist, the upper line of the dulness limit slopes upward toward the spine, but the sign is not the characteristic one to which Grocco called attention.

CASES OF PLEURAL EFFUSION IN WHICH GROCCO'S TRIANGLE IS NOT DEMONSTRATED

The literature cites many cases in which puncture has disclosed free fluid in the pleural sacs, but previously, the paravertebral dulness could not be determined. In the majority of these instances it was not proved that the exudate in question extended mesially as far as the vertebral column. It would seem, from the nature of the anatomic relations existing, that only when the spine is intimately related to airless tissue—a pneumonia, a mediastinal tumor, an enlarged heart, a collection of abnormal lymph-glands or fluid—can one logically expect the diminution or loss of vertebral resonance. In one of our cases a needle clogged with fibrin was responsible for a negative tapping. In this case the physical signs, apart from the paravertebral triangle itself, were characteristic. A short needle or a worthless aspirating syringe may be similarly responsible for a "dry tap."

THE PRESENCE OF PARAVERTEBRAL DULNESS IN CASES IN WHICH THE PATHOLOGIC CONDITION EITHER IS NOT PRIMARY IN THE PLEURAL SAC OR IS EXTRATHORACIC

In the consideration of these conditions it should be plainly understood that the paravertebral triangle of percussion dulness, as brought into prominence by Grocco as a valuable sign in pleural exudates, has certain well-defined characteristics. It is a triangle whose perpendicular side is generally greater than its base; it is a sign usually associated with demonstrable alterations on the opposite side of the thorax to that on which the triangle can be demonstrated; that these signs on the opposite side are those, as a rule, of pleural exudate; that the triangle of Grocco is one that varies in extent with the position of the patient, *e. g.*, may disappear when a patient lies on the fluid-containing side and reappear when the patient again assumes the upright position; that the sign disappears in unilateral effusions when the pleural fluid disappears or is in diminished amount; that over the paravertebral area of dulness there are frequent well-defined auscultatory findings.

Dulness along the spine has been described in pneumonia, in tumor of the lung, mediastinal tumor, and markedly enlarged heart or diseased peribronchial or mediastinal lymph tissue. It should be pointed out that only rarely in these examples does the paravertebral area of dulness approach a triangle in shape, and never does it satisfy the requirements stated in the preceding paragraph.

In certain extrathoracic conditions attention has been called to the presence of paravertebral dulness in the thoracic zone. In all the instances cited, however, the dulness has not been associated, primarily, with a thoracic pathology. The abdominal alterations have been usually marked. Ewart's discovery of the triangular areas of dulness along the spine in ascites has already been dwelt on. In these instances, evidences of abdominal disturbance are not lacking, even though the paravertebral dulness can be made to change with alterations in the position of the subject. In the cases of subphrenic abscesses associated with spinal dulness in the thoracic region the triangles were atypical and the abdominal symptomatology was marked. The cases of multilocular cystadenoma and advanced pregnancy reported by us were associated with an appearing and disappearing triangle of dulness, but in all instances the signs of effusion in the pleural sacs were absent. The same applies to Landa's reports.

It would appear that the evidence furnished by paravertebral dull areas in extrathoracic disease is of value in determining the lower thoracic abdominal boundaries, posteriorly—a field of observation which, up to the present, has been greatly neglected in routine examination. Perhaps one of the greatest benefits that will accrue to the diagnostician from a consideration of the work of Grocco and others is that of receiving a stimulus to make greater effort to regularly determine the limits of thorax and abdomen accurately, posteriorly, in all instances where physical signs point to thoracic or abdominal disease with fluid.

SUMMARY

1. In cases where fluid exists in a pleural sac and this fluid impinges upon the spine, it is possible to map out, in the average patient, an area of percussion dulness on the side of the spine opposite to that on which effusion may be demonstrated. This paravertebral area is an area of relative dulness, and is roughly triangular in outline. It may disappear when the patient changes position, or it may in that event be altered in shape or extent. The tri-

angular area is frequently associated with auscultatory findings similar to those existing in connection with pleural exudate or lung tissue whose air content is altered.

2. Paravertebral dulness may be the result of physical or pathologic conditions other than pleural effusion. These may be intrathoracic or extrathoracic. In intrathoracic disease, as pneumonia, mediastinal tumor, lung abscess, and the like, dulness to the opposite side of the spine may be definitely determined. This dulness usually does not satisfy either the physical phenomena or the clinical requirements associated with paravertebral dulness due to free fluid in the pleural sac. The same may be said of paravertebral dulness associated with extrathoracic conditions, *e. g.*, ascites, subphrenic abscess, abdominal tumor, etc.

3. A certain amount of experience with the sign and skill in thoracic percussion is requisite for its proper demonstration. Even where more than common skill is available, the presence of thick parietes, fibroid pleura, improper position of the patient, etc., may mask the area of paravertebral dulness associated with pleural exudate reaching mesially to the vertebral column.

NOTE.—The work outlined in this paper was begun in the Medical Clinic of the University of Michigan, service of Professor George Dock, in 1907.

REFERENCES

1. Da Costa: "Amer. Jour. Med. Sci.," December, 1909, p. 815.
2. Pottenger: *Ibid.*, October, 1909, p. 520.
3. Cabot: *Ibid.*, December, 1909, p. 813.
4. Grocco: "Riv. crit. di clin. Med.," 1902, Nos. 13 and 14.
5. Rauchfuss: "Gerhardt's Handbuch der Kinderkrankheiten," 1878, vol. iv.
6. Weil: "Handbuch der topographischen Perkussion," 1880.
7. von Korànyi: "Wien. klin. Rundschau," 1902, vol. xvi, p. 300.
8. See ref. No. 4; also "Riv. crit. di clin. Med.," Florence, 1909, vol. x, p. 1.
9. Flora: Riv. crit. di clin. Med.," Florence, 1902, No. 19.
10. F. Maragliano: "Bull. della Soc. Eustachiana," 1903, Nos. 1 and 2.
11. G. Pierracini: "Clin. Med.," Pisa, 1903, Nos. 5, 8, and 9.
12. Bucco: "Cron. clin. Med. del Prof. De Renzi," Naples, 1903, p. 6.
13. Baduel and Siciliano: "Riforma med.," Palermo, 1904, Nos. 20 and 35.
14. Padoa: "Gazz. do osp.," Milan, 1907, No. 28, p. 342.
15. Cecchini: "Riv. crit. di clin. Med.," Florence, 1904, No. 5.
16. P. Pennato: *Ibid.*, Florence, 1909, No. 10, p. 68.
17. Siciliano: *Ibid.*, Florence, 1908, No. 9, p. 749.
18. Banti: "Riforma med. di Palermo," 1904. (See "Jour. Amer. Med. Assoc.," 1904, vol. xliii.)
19. Silvestri: "Policlinico," Rome, 1904, No. 14, p. 869.

20. Ferrannini: "Riforma Medica," August 30, 1904.
21. Ewart: "Lancet," London, 1905, vol. ii, p. 216.
22. Ewart: *Ibid.*, 1907, vol. i, p. 1771; also vol. ii, pp. 49 and 188.
23. Ewart: "Progressive Medicine," 1907, vol. ix, p. 40.
24. Forbes-Ross: "Lancet," London, 1907, vol. i, p. 1773.
25. Morison: *Ibid.*, 1907, vol. ii, p. 114.
26. Smith: *Ibid.*, 1907, vol. ii, p. 890.
27. Rauchfuss: "Deut. Arch. klin. Med.," 1906, vol. lxxxix, p. 186.
28. Weitz: *Ibid.*, 1908, vol. xcii, p. 526.
29. Jamburger: "Wien. klin. Wochenschr.," April 15, 1906.
30. Goldscheider: "Berlin. klin. Wochenschr.," 1910, vol. xlvii, p. 187.
31. Aroaz: "Rev. Soc. med. Argentina," 1906, p. 289.
32. Pruneda: "Escuela de med.," 1908, No. 16.
33. Landa: "Rev. Med.," Mexico, 1908, No. 9, p. 388.
34. de Barros: "Presse méd.," Paris, 1909, No. 27, p. 240.
35. Roch and Dufour: "Semaine méd.," Paris, 1908, vol. xxviii, p. 505.
36. Cassaet: "Clinique," Paris, 1908, vol. iii, p. 675.
37. Brudzinski: "Arch. de méd. de enfants," Paris, 1909, vol. xii, p. 188.
38. Thayer and Fabyan: "Amer. Jour. Med. Sci.," January, 1907.
39. Frankenheimer: "California State Jour. Med," 1907, vol. v, No. 9, p. 224.
40. Reilly: "Arch. Diagnosis," New York, 1908, vol. i, No. 1.
41. Blumer: "Trans. Conn. State Med. Soc.," 1908, p. 237.
42. Gordinier: "Albany Med. Ann.," April, 1909, p. 324.
43. Beall: "Jour. Amer. Med. Assoc.," 1908, vol. li, p. 1016.
44. Calvert: "Amer. Jour. Med. Sci.," August, 1908.
45. Smithies: "Physician and Surgeon," Ann Arbor, 1908, No. 4.
46. Smithies: "Jour. Amer. Med. Assoc.," May 9, 1908, p. 1491.
47. Smithies: "Amer. Jour. Med. Sci.," October, 1908.
48. Smithies: "Jour. Mich. State Med. Soc.," March, 1909.
49. Barbieri: "Rendica Ass. med. di Parma," 1904, vol. iv, p. 60.
50. Ghelfi: "Contributo clinico del Parma," Rome, 1904.
51. Signorelli: "Policlinico," Rome, 1902, No. 31.
52. Plessi: "Riv. crit. di clin. Med.," Florence, 1905, vol. vi, p. 411.
53. Grocco: "Riforma medica," Naples, January, 1911, No. 1; "Wien. klin. Wochenschr.," May 11, 1911, No. 19.
54. Ferrannini: "Riforma med.," June 19, 1911.

SACROCOCCYGEAL SINUS (POSTANAL DERMOID): A REVIEW OF 31 CASES*

H. Z. GIFFIN AND ALEXANDER ARCHIBALD

In all branches of medicine the superficial and apparently simple conditions have been least attractive for careful clinical study, and, as a consequence, our knowledge concerning them has been insufficient. In view of this fact it may be of some value to consider the characteristics of sacrococcygeal sinuses and cysts.

One is, as a rule, open to grave error in obtaining the results of former examinations directly from patients. However, it is evident, from the histories obtained in these cases and from the character of the operative procedure which had been followed, that the sacrococcygeal sinus of a postanal dermoid is at times not recognized. As accurately as can be judged, not more than 4 of the 31 cases herewith reported were diagnosed elsewhere as postanal dermoid. Ten had been treated previously at other clinics. Of these, 4 had been incised and drained, 2 cureted, 2 had been treated by injections of bismuth emulsion and one by injections of carbolic acid. Excision had been attempted in only a single instance.

A full discussion of sacrococcygeal, presacral, retrorectal, and rectal dermoid tumors and of teratomas will not be undertaken in this paper. These various tumors are related to the sacrococcygeal sinus and are extremely interesting from an embryologic standpoint.

The explanations of the origin of the various types of these tumors have differed somewhat, but in general the embryologic development is as follows: Growth is more nearly perfect as well as more rapid in the upper part of the embryo. Closure of the medullary tube proceeds from the cervical region downward. The medullary tube at first extends the full length of the protovertebral column, and the spinal portion of the medullary canal in the caudal extremity remains for a time an open rhomboid dilatation. The medullary tube has been found in the form of a cylinder in the cervical region of the human embryo at four weeks. The lower end of the tube has been found ununited at the ninth week, this portion being slightly enlarged, and presenting a longitudinal median slit analogous to the rhomboid sinus in birds. The filum terminale is the result of a more rapid growth of the spinal column than of the spinal cord. At the level of the middle of the sacrum the filum terminale perforates the dura mater and passes on to be attached to the periosteum over the coccyx at the lower end of the sacral canal. In other words, if the lower end of the medullary canal did not close, the opening would be situated in the median line at the lowest portion of the sacrum or over the coccyx. This is the point at which the sacrococcygeal dimple is found. The mesoblastic tissue which extends backward between skin and closed medullary canal is very thin in this region and the skin may be attached directly to the periosteum (Figs. 204 and 205).

---

* Reprinted from "The Archives of Diagnosis," April, 1912.

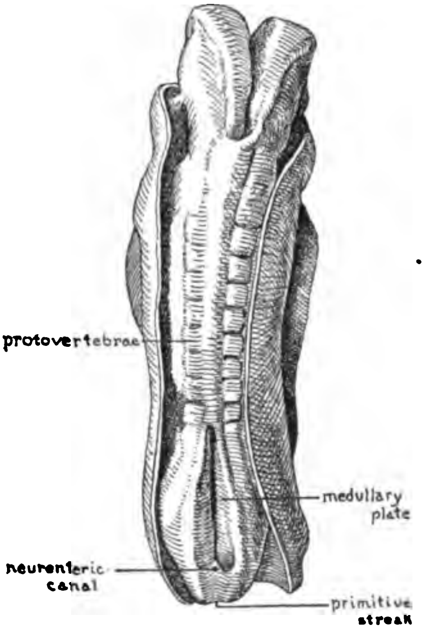


Fig. 204.—The anlage of the central nervous system of a human embryo 2.11 mm. long (about thirteen to fourteen days old) (redrawn from Kollmann's "Embryology" after Eternod).

(1) Inclusions of epidermoid cells in the mesoblastic tissue near this point of late closure doubtless explain the origin of sacrococcygeal dermoids and sinuses. These inclusions probably

originate from the coccygeal or caudal remnant of the neural canal rather than the anterior or neurenteric remnant. Mallory* examined by serial section this portion of seven fetuses from three to six months old. In these he was able to demonstrate over the coccyx canals lined with epithelium, some of them being connected with the skin.

(2) The obliterated neurenteric canal and postanal gut doubtless account for a second group of tumors in this region. The medullary and alimentary tubes are continuous at the caudal extremity of the embryo through the neurenteric canal. When the proctodeum invaginates to form the cloaca it meets the intestinal tube anterior to the opening of the neurenteric canal. The resultant portion of the bowel posterior to the anus has been termed the postanal gut. Tumors of the postanal gut proper seem to have a constant pathologic structure. They are cystic in character, lined with glandular, epithelium, and contain a glue-like fluid. Postrectal and rectal dermoids may originate from cell inclusions in the tract of the obliterated neurenteric canal, and, although generally existing as tumors, may present external fistulas.

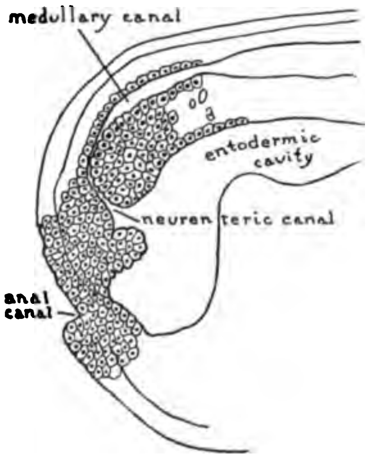


Fig. 205.—Sagittal section of frog's ovum shortly after closure of medullary groove. The anal canal is only partially cut, but was found open in neighboring sections (redrawn from Durham).

(3) Teratomas, containing the tissues and the fragments of viscera of a suppressed fetus, are fairly common in this region. Large tumors of this type have been reported. These have been regarded as true parasitic double formations or as the result of a tendency of the caudal node to develop after the manner of the cephalic node.

---

* Mallory: "Amer. Jour. Med. Sci.," 1892, vol. ciii, p. 263.

(4) An implantation cyst or traumatic dermoid following a penetrating injury may occur in the region of the sacrum. Implantation cysts are the result of traumatic inclusions of epithelium and hair-follicles, and are usually of small size in man. They are found more frequently in beasts, especially as a result of prodding, and in them often attain a large size. One case is herewith reported.

(5) A rare type of tumor over the sacrum has been described (Bartel, "Ein Beitrag zur Kasuistik der Tumoren der Sakralgegend"). It is composed of small cysts lined with epithelioid cells and containing cholesterin crystals and a broth-like fluid.

(6) Fistulas lined with epithelium and originating from diverticula of the anal portion of the rectum may open externally and differ little clinically from an ordinary anal fistula. (This subject will be reviewed in a later paper.)

(7) Ischiorectal abscess, anal fistula, and tuberculous sinus complete the list of conditions which must be kept in mind.

The coccygeal dimple is very common in man. It may be definite in one out of every five male patients examined, and often amounts to an infundibulum. A thickened subcutaneous cord can be felt leading from this dimple in many of the cases. One cannot say that the presence of a dimple or subcutaneous thickening means that cell inclusions are present, but if present, they await only trauma, irritation, or infection to produce symptoms. Hair and sebaceous material within these sinuses and inclusions may be an element in the causation of infection, inflammation, and tumor formation. Epithelium may have originally been present, but as a result of inflammation the epithelial lining has generally been destroyed and hair may be absent.

From January 1, 1906, to January 1, 1912 (the last case was dated August 2, 1911), 31 cases of sacrococcygeal dermoid have been operated on in the Mayo Clinic. All but one of these were sacrococcygeal sinuses at the time of operation. Of the 31 patients, 2 only were females. One patient was operated on at the age of thirteen, and 2 at forty-six and forty-nine years respectively. The remaining 28 were quite evenly distributed between the ages of fifteen and thirty, the average age being twenty-four.

In 26 of the 31 cases the patient's attention was first attracted by a painful, swollen area behind the anus. The remaining 5 had first noticed a thin, watery discharge for which there had been no apparent cause. In all those in the first group save one rupture followed. In 12 of the total number it was noted that the discharge was intermittent, and pain, tenderness, and swelling were complained of when the sinus was closed. In 30 of the 31 cases the discharge was the chief complaint at the time the patient presented himself for examination. In one case a tumor the size of a small egg had been present for six years and had not ruptured. This is the only unruptured dermoid in the series.

The duration of discharge varied from two months to ten years. Eight had been discharging more than five years. Of the remainder, 15 more than one year and 7 less than one year.

Six of the patients gave a definite history of injury directly preceding the onset of symptoms. It is quite likely, however, that traumatism is a more prominent factor than this number would indicate. Injury sufficient to favor infection might go unnoticed. Several of the histories suggested the possibility that continued rubbing and scratching may have been an etiologic factor.

In 20 a single sinus was present. In 6 there were 2 sinuses, and in 4, 3 sinuses. One patient presented an unruptured tumor.

In 25 the opening of the single sinus or one at least of the multiple sinuses was situated in the midline between the coccyx and anus. This location is important evidence in the diagnosis. In only 5 of the 20 cases in which there was a single sinus was the opening to the side of the midline. In only 3 of the 10 cases with multiple sinuses was there one or more openings to the side of the midline.

In one case there were 2 sinuses which opened just above the tip of the coccyx. In another case with 3 sinuses, 2 of them opened at the midpoint of the sacrum. In 3 cases one of the openings was over the sacrum. In a case with 2 sinuses one sinus ran far out into the left buttock, and this evidently led to a diagnosis of tuberculous fistula.

The presence of hair was noted in only 6 cases. A very small amount of hair is easily overlooked, and if not removed, may be a cause of imperfect healing. The sinuses were found to run toward the coccyx or lower sacrum in all cases that were probed. These findings should be regarded as most important in the diagnosis.

In addition to the cases reviewed, one patient has been seen with an *implantation cyst* over the sacrum. She gave a history of a penetrating wound caused by sitting upon a crochet-needle five years previously. A swelling had appeared and disappeared several times. The wound had failed to heal after drainage at another clinic, and a sac containing pus was excised at operation.

A clinical diagnosis of postanal dermoid was made in 26 of the 31 cases. Two were diagnosed as tuberculous sinus, 1 as ischiorectal abscess, and 2 as anal fistula.

Excision and drainage were done in all the cases. Bismuth injections were tried before operation, in one without beneficial results. There were no deaths following operation.

Reports have been received concerning the patient's condition in 20 cases. In 15 of these the wound healed and remained healed. Five have not healed; one of the 5 has since been operated upon 3 times, and has failed to heal even temporarily. The remaining 4 have not had a second operation. In 11 of the 15 cases permanently healed the exact date of healing is known. Four weeks is the earliest time, and sixteen weeks the latest, the average being eight and one-half weeks.

Surgery may fail because the condition has been treated in some other way than by careful excision of the sac. To obtain all the lining membrane is essential. A diagnosis may not have been made, and consequently an abscess may be drained, a sinus cureted, or an effort made to effect a cure by non-surgical measures. Two or 3 sinuses or inclusions may be present, and only one found and dissected out. A small amount of hair remaining in the tissues may prevent permanent healing.

DIAGNOSIS

The diagnosis of the fistula of sacrococcygeal dermoid is, as a rule, in no way difficult. It is chiefly necessary to have the relative frequency of the condition in mind. The demonstration of a sinus opening in the sacrococcygeal region or between the coccyx and anus, which, upon probing, leads in the direction of the lower sacrum and coccyx, is usually sufficient evidence. The presence of the dimple in addition to the sinuses is confirmatory evidence. A fibrous subcutaneous thickening along the sinus and over the sac can usually be palpated. The opening of the sinus is generally in the midline. Hair may be obtained in only a small percentage of the cases, probably because of the fact that secondary inflammation has taken place. If the postanal tissues are put on the stretch by pressing the buttocks apart, the dimple and subcutaneous tract will be more clearly demonstrated.

The condition is often mistaken for anal fistula, generally because of superficial examination. Probing of the sinus of anal fistula will usually show clearly any relationship to the rectum, and the probe can be felt by the finger introduced into the bowel. The blind sinus of an ischiorectal abscess will run deeper into the tissues of the pelvic outlet. A tuberculous sinus is more apt to show sluggish gray granulations, and there may be evidence of tuberculosis elsewhere. A postanal sinus may rarely communicate with a precoccygeal or presacral dermoid.

An unruptured postanal dermoid may be more difficult of diagnosis, especially if a secondary abscess has formed. Ischiorectal abscesses which result from infection from the bowel will usually extend into the deeper tissues. A history of intermittent swelling and pain, over a period of years, and the superficial location of the tumor, will generally differentiate the condition.

REGENERATION OF THE TENDONS*

M. S. HENDERSON

It is my purpose to present a brief report of the results following experiments made on a series of dogs, with a view to demonstrating the regenerative power of the tendons. A very brief review of the literature on the subject will be made.

Interest in the surgery of tendons was probably first keenly awakened when, in 1880, Nicolodoni sutured the tendon of a functionating muscle to the tendon of a paralyzed muscle. This in itself was not successful, due to the stretching of the paralyzed tendon, but it encouraged other observers to take up work along these lines.

Drobnik and Lange developed the periosteal insertion of the transplanted tendon, now considered so essential to a functional result, and in 1902 Lange reported a case two and one-half years after operation. In this patient, a male, the quadriceps tendon had been lengthened, a functionating tendon resulting.

Borst, Seggle, Rydygier, and Vulpius are among those who have investigated this subject. In this country James Warren Sever has given us several excellent papers. He reports a series of experiments on cats, and demonstrates the practicability of bridging defects of the tendons with silk suture, and has shown the influence the sheath has on regeneration of the tendon. F. L. Richardson, in his paper on "Tendon Suture," gives a concise description of the process of the repair of tendons. In a recent article by Lewis and Davis the question of direct transplantation of the tendon was discussed, and they report having transplanted pieces of the tendo Achillis 1¼ to 1½ inches long from one dog, to fill in a defect in the tendon of another dog. Uniformly good results were obtained by them, which establishes the possibility of this direct transplantation.

---

* Read before the Amer. Orthopedic Assoc., Atlantic City, June, 1912. Reprinted from "Journal-Lancet," March 15, 1913.

Tendon, in common with other forms of connective tissue, such as fascia, sclera, ligaments, cartilage, bone, and dentin, arises from mesoblastic tissue. It is composed of bundles of white fibrous tissue containing few cells, and is invested with a layer of loose connective tissue called the peritendineum, which is quite freely supplied with blood-vessels and nerves. This peritendineum dips in between the bundles of white fibrous tissue, and carries with it the nerve- and blood-supply to the body of the tendon. It is claimed that the regenerative power of the tendon comes from this peritendineum and the septa which it sends between the bundles of fibrous tissue into the interior of the tendon. A simile is drawn, likening it to the periosteum and the endosteum of the bone.

In the series herein reported the work was done on the tendo Achillis. Large dogs were used, for the reason that in the larger animals a sheath was demonstrable, and with its peritendineal structures was of sufficient strength to allow suturing, whereas in the smaller animals it was found difficult to demonstrate a sheath of sufficient strength to allow of manipulation. The tendo Achillis in the dog consists of three tendons. Each has a separate sheath, and the whole is invested in a common sheath and peritendineum.

The suture material used to bridge the defects was black linen—black for the reason that it is more easily traced when the dissections are made later. Two strands were the most used, the purpose being to provide a scaffolding on which repair could take place. In the dogs in which the sheath was saved it was always closed with plain continuous catgut sutures. The skin was sutured with plain catgut.

At the end of the operation a plaster-of-Paris cast was applied from the toes to the groin. This was removed in two weeks, after which time the dogs were allowed to run at will in their pen.

These dogs were all operated on under morphin, followed by Thompson's fluid, which produced satisfactory and complete anesthesia. The dogs were killed with chloroform at the end of six months; the legs were amputated, and macroscopic and microscopic examination made. The microscopic examinations were not particularly enlightening. MacCarty made a study of the specimens with me, and we attempted to make a distinct differentiation between true tendon and connective tissue. This was possible only in a few well-marked instances. Macroscopically, true tendon appears as a white, glistening cord. Ordinary connective tissue does not possess this glistening appearance. These bundles could be traced in the functionating regenerated tendons, whereas they were absent where there was an anatomic, but no functional, restoration. In none of the animals in which the sheath was removed was there a well-marked, freely movable sheath, as there is normally. In those in which the sheath was not removed there was a nearer approach to the normal, though even here the sheath was more or less adherent. In the dog in which no linen was inserted to bridge the defect and the sheath was carefully sutured over the space with catgut, there was an anatomic restoration more nearly normal than in those in which the linen was inserted. The linen seemed to act as a foreign body, causing great proliferation, evidenced grossly by the increased size of the tendon.

In one dog linen was inserted high upon the tendon, and carried down the outside, to be inserted into the periosteum. There was great proliferation macroscopically, and microscopically many giant-cells were present. In this instance there was apparently an unsuccessful attempt to absorb the linen.

Linen was used in three of the animals. In two the linen was used to bridge a defect caused by the removal of a piece of tendon. In the first dog the sheath was left, and sutured over the two strands of bridging linen. In the second the linen was left uncovered by the sheath, the sheath and peritendineal structures being removed along with the piece of tendon. In both there was complete restoration of function. On dissecting the specimens only knots of the linen were found. On such scant data, however, we do not wish to state that the linen was absorbed. We have other experiments under way to prove this point. The third dog in which linen was used is the one heretofore described, in which there were great proliferation and numerous giant-cells.

Eight dogs were operated on in this series, but only 5 of them could be used for observation. One died before the experiment could be of value. In one the wound became infected. The third was eliminated because no definite record had been kept of the conditions.

Dog No. 148 (see photograph of specimen, Fig. 206): One and one-half inches of tendon were resected, and the sheath left. Nothing was used to bridge the defect except that the sheath was closed with continuous plain catgut suture. Complete anatomic and functional restoration.

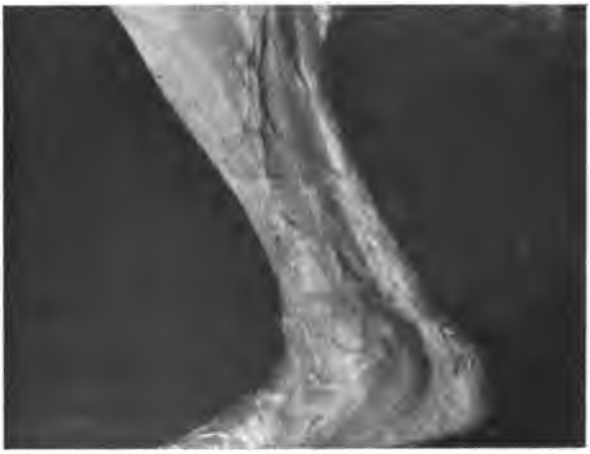


Fig. 206.—Photograph of specimen taken from dog No. 148. One and one-half inches of tendon resected and sheath left. Complete anatomic and functional restoration at the end of thirty days. Note the difference between this posture and that of dog No. 146, where the sheath was not left.

Dog No. 146 (see photograph of specimen, Fig. 207): Removal of one and one-half inches of tendon and sheath. Nothing used to bridge the defect. There was a filling in to restore the anatomic defect, but this pseudotendon never functionated.

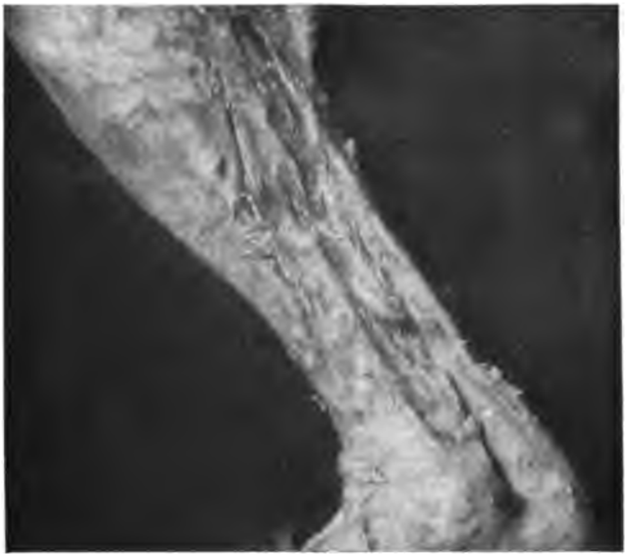


Fig. 207.—Photograph of specimen taken from dog No. 146. Removal of 1¼ inches of tendon and sheath. Nothing used to bridge the defect. A poor anatomic with no functional restoration at the end of six months. Note the difference between photograph of this dog and those of dogs Nos. 144 and 142.

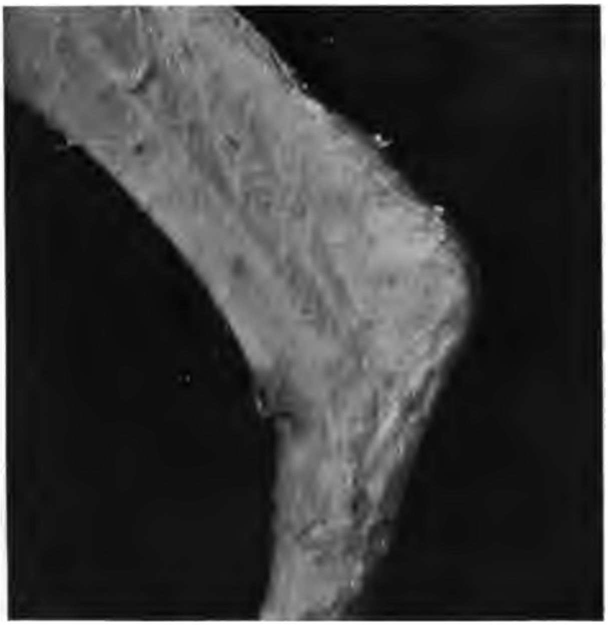


Fig. 208.—Photograph of specimen taken from dog No. 144. Removal of 1½ inches of tendon, leaving the sheath. Linen used to bridge the defect. There was complete anatomic and functional restoration at the end of thirty days. Note the thickened "new tendon." Normal use in about thirty days after operation.

Dog No. 144 (see photograph of specimen, Fig. 208): Removal of one and one-half inches of tendon, leaving the sheath. The defect was bridged with two strands of linen, and the sheath sutured over the space with plain catgut. There was anatomic and functional restoration.

Dog No. 142 (see photograph of specimen, Fig. 209): Removal of one and one-half inches of tendon with the sheath. The defect was bridged with two strands of linen. There was anatomic and functional restoration.

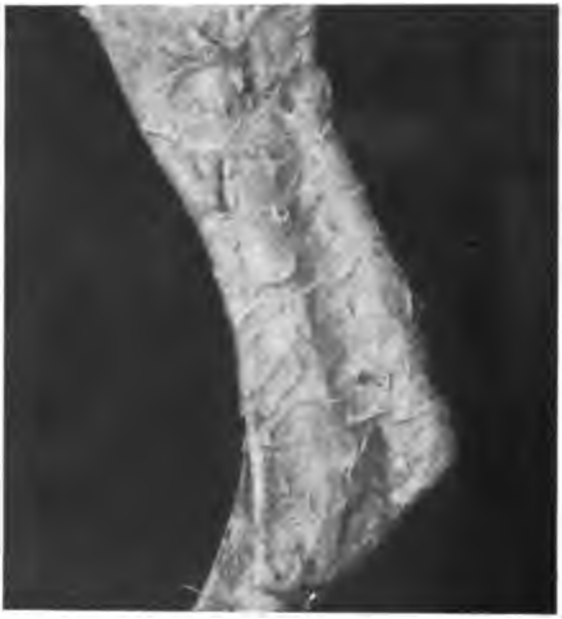


Fig. 209.—Photograph of specimen taken from dog No. 142. Removal of one and one-half inches of tendon with the sheath. Linen used to bridge the defect. Complete anatomic and functional restoration at the end of thirty days. Cast removed in two weeks, and dog gradually began to use the leg; one month after operation used practically to normal extent. Note the regenerated portion which shows up thicker than the old portion.

Dog No. 147: Piece of linen put through the tendon high up, and carried down to a periosteal insertion in the heel. Great proliferation occurred about the linen, showing microscopically many giant-cells, the result of the chronic irritation produced by a foreign body.

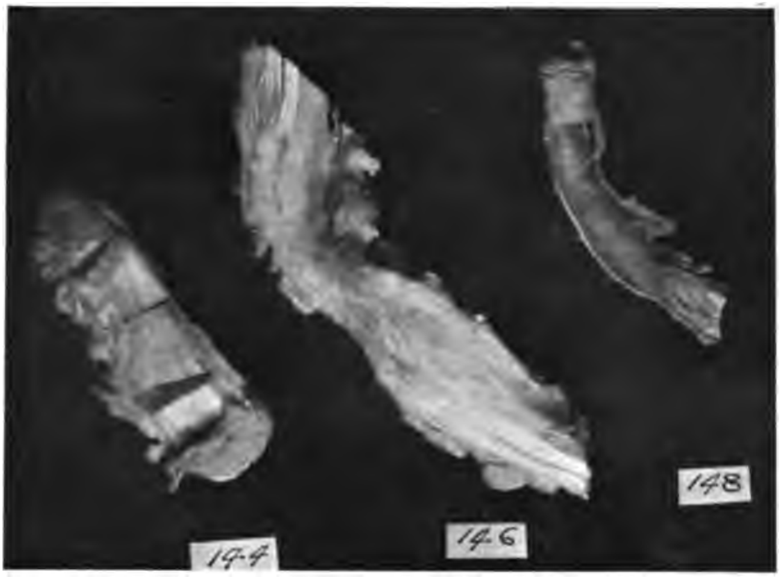


Fig. 210.—Photograph of long section of specimens. Note Nos. 144 and 148 show glistening fibers running through mass of fibrous tissue. No. 146 shows anatomic restoration, but not functional. Note dull appearance of fibrous tissue filling gap between ends of tendon.

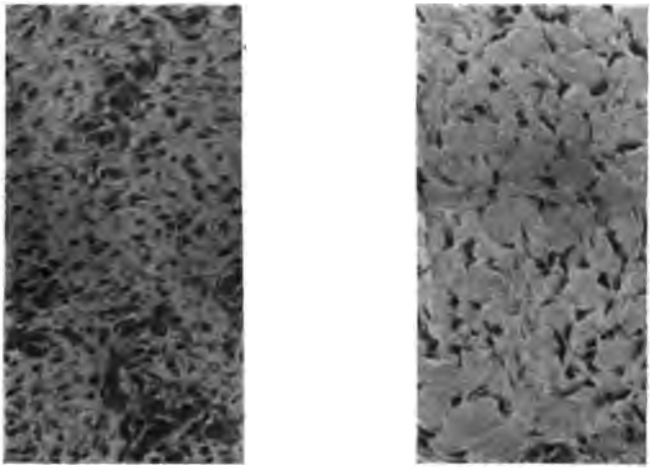


Fig. 211.—Microphotograph for comparison. The photograph on the left shows ordinary scar tissue, the free blood-supply, and irregular arrangement of cells. The microphotograph on the right shows true tendon. Note the more regular arrangement of cells and absence of blood-vessels.

REFERENCES

Borst: "Sitzungsb. d. phys.-med. Gesellsch. zu Würzb.," 1903, pp. 22–26.
Drobnik: "Deut. Zeit. f. Chir.," vol. vii, p. 1.
Lange: "Zeit. f. orthop. Chir.," 1903–4, vol. xii, pp. 16–44.
Lewis and Davis: "Jour. Amer. Med. Assoc.," vol. lvii, August 12, 1911.
Nicolodoni: Vulpius: "Sehnenüberpflanzungen," Leipzig, 1902.
Rydygier: "Sitzungsb. d. phys.-med. Gesellsch. zu Würzb.," 1903, p. 79.
Sever: "Boston Med. and Surg. Jour.," May 25, 1911, vol. clxiv, pp. 748–752.
Seggle: "Beitr. z. klin. Chir.," vol. xxxvii, H. 1–3.
Richardson: "Boston Med. and Surg. Jour.," vol. clxiv, pp. 752–754.
Vulpius: "Die Sehnenüberpflanzung," 1902.

THE OPEN TREATMENT OF FRACTURES*

E. H. BECKMAN

There is no subject in medicine of more wide-spread interest than the subject of fractures. Nearly every practitioner is called upon at some time to treat this condition, and then realizes the great responsibility which he carries. Many of us have felt the lack of security and ability to deal with fractures that we feel in other lines of our work, and if we ever long intensely for eyes in our finger-tips, it is in diagnosing and treating fractures. It is not strange, then, that a revival of interest in the subject should be periodic, or that some new method for the treatment of this condition should be productive of much literature and spirited discussion. One has but to glance at the medical journals of today to realize the interest taken by the medical profession in this subject. The reason for this interest has developed from several causes. The advances made in *x*-ray work have shown us our errors in reducing and treating fractures with such positive evidence that no ground for argument is left. It has also shown that nature comes to the physician's rescue in bone work as often as in other lines of medicine, and that her efforts at rounding off angles, strengthening weak areas, and readjusting the skeleton are necessarily slow, but exceedingly efficient.

There is a feeling among physicians that the operative treatment of fractures has not made the same rapid advance as have other lines of aseptic surgery. The splendid work of Arbuthnot Lane in demonstrating the value of common steel plates and screws in the repair of fractures, and his belief that all fractures should be treated by the open method, have been potent factors in stimulating interest in the subject. These are but a few of the causes which have at the present time revived the interest in the open treatment of fractures. The many valuable papers on the subject by American surgeons have brought about a fairly well-established basis for the method. This ground, as expressed by the majority of our leading surgeons, is essentially as follows:

---

* Read before the Southern Minn. Med. Soc., August 6, 1912. Reprinted from "The Journal-Lancet," April 1, 1913.

Every case of fracture must be considered individually as to whether or not a better result can be obtained by non-operative or by the operative treatment. I can give no better idea of what I mean than by quoting the words of Dr. Blake,* who says: "As to what constitutes a reasonable doubt as to the ultimate results from non-operative treatment, depends so much upon the thousand and one conditions that may be present in the patient, and also upon the ability of the surgeon to meet them, that it is practically impossible to state in so many words what fractures should be treated without and what by operation. Again, one surgeon may be able to do rapidly, accurately, and cleanly what would be practically impossible for another; so that there are considerations to be taken into account other than the conditions present in the patient. In fact, there is no province of surgery in which the results depend more upon the mechanic skill and cleanliness of the operator."

Most fractures can be successfully reduced and retained in position, so that an open operation is not necessary for a good functional result. If a fracture cannot be reduced and retained in position by the ordinary means at our disposal, it should be treated by the open method to accomplish this reduction, provided a reliable surgeon can be obtained and the patient's condition will warrant it.

There is no emergency in which the final results depend more upon the intelligence and painstaking attention to details by the physician than the care of fractures. Two x-ray photographs, taken at planes 90 degrees to each other, should be taken of every fracture where possible. Every physician who has sustained a fracture himself, no matter how much confidence he had in his surgeon, usually insists upon an *x*-ray photograph. He should be anxious to allow his patient the same privilege.

---

* "Surg., Gyn. and Obst.," April, 1912, p. 338.

Many compound, comminuted fractures with considerable mutilation of the soft tissues are best treated by immediate operation, which allows the small fragments of bone to be removed, which provides for the removal of soft parts that may be interposed between the fragments, as well as some form of fixation being applied to the remaining bone, if necessary. The patient is thus saved much time and a better final result obtained.

If an operation is necessary, the time of operating and the condition of the patient are important factors. Most physicians agree that an operation immediately following a fracture is often necessary, but when three or four days have elapsed and there is a great deal of edema of the soft parts, it is wiser to wait until this extreme swelling has subsided. The tissues are then in better condition to resist infection and stand added traumatism.

The technic of operation that has been worked out by those who do a great deal of bone work has had no small part in producing the many brilliant results obtained. All surgeons agree that asepsis is of extreme importance, and that an operation should rarely be undertaken unless the conditions for avoiding infection are present. After the incision is made the edges of the incision and the skin should be carefully covered with towels or cloths moistened in salt solution, to prevent infection from the edges of the wound and skin being carried to the deeper parts of the wound. The incision should be planned to avoid the more important nerves and blood-vessels, and to allow the exposure of the fracture with as little traumatism to the overlying muscles as is possible. The periosteum should be saved wherever possible. If it be necessary to place a plate or other mechanic appliance on the bone to retain the fragments in position, it should be placed on top of the periosteum and not underneath it. The pressure from this appliance, which theoretically would cause a degeneration of the periosteum, does not often do so.

Every mechanic appliance which is intended to remain permanently in the wound should be applied so that it is absolutely immovable, since it has been demonstrated that its tendency to work loose and require later removal is much less if so applied. No antiseptic should be used in the wound when a foreign body is to remain on the bone permanently, as this had a tendency to produce oxidization and to bring about a condition which will later require removal of the retaining substance. Drains should be avoided, if possible.

Steel plates have less tendency to work loose and require later removal if placed so that they are covered to a considerable depth in the soft tissues. When placed so they have only the skin covering them, they nearly always require removal at some later period.

Hemorrhage should be carefully controlled, and all dead space obliterated in order that the circulation be taxed as little as possible. We believe that most American surgeons prefer a light retention dressing of some kind on all fractures that have been operated on. A light plaster-of-Paris cast is our preference. It is often well to split this cast immediately to avoid pressure from swelling which may occur.

All surgeons who are operating on fractures agree that the instruments which have been developed by the present revival of interest in this line of work are exceedingly valuable; that they accomplish their purpose well, and are the most satisfactory of any devised so far for the purpose.

The long forceps used for steadying and tracting upon the shafts of bone prevent much mutilation of the soft parts, eliminate the necessity of putting the hand into the wound often, and shorten the operation considerably. The apparatus for producing traction to overcome shortening and the overlapping of the fragments in long bones, such as that devised by Martin, Bartlett, Magneson, and others, is of great value, especially in old fractures.

No discussion of the open treatment of fractures would be complete without making mention of the steel plates and screws devised by Arbuthnot Lane, although it should be remembered that they are but one of the valuable appliances for retaining fractures in position. It has been demonstrated that common steel plates, wire, screws, and nails are better than the silver previously used, since they are stronger and do not irritate the tissues to a great extent. When the plates are used, they should be of good material, to minimize the danger of their being broken.

An open operation does not necessarily mean that some foreign material must be left in the wound after reduction, since the fragments can often be retained in position without such an appliance. The steel plates are especially valuable on the shafts of long bones, and are being used more and more as experience demonstrates their efficiency. Foreign material should not be left in close proximity to a joint, as the callus and the appliance itself may interfere with perfect movement.

Fractures of the clavicle, Colles' and Pott's fractures rarely require open operation. Fractures of the patella nearly always are best treated by open operation. The operation of Blake, which consists of suturing the periosteum and soft tissues without any retention apparatus securing the bone, is perhaps the best operation, although a wire or suture incircling the fragments is sometimes necessary. Fractures of the hip-joint, when requiring open operation, are treated most successfully by using nails or screws instead of wire or plates. Fragments of the shafts of the long bones, when requiring operation, can be retained in position more securely by a plate and screws than by any other method yet devised, but a plate is not always applicable, and at the time of operation the kind of retention apparatus best suited to the case must be selected. Fractures about the elbow seldom require operation unless the olecranon is broken off or the head of the radius displaced. Suturing the olecranon with chromic catgut serves to give the best results.

AN UNUSUAL BONE TUMOR OF THE FOOT*

E. H. BECKMAN

This case is reported because of the unusual circumstance of finding a bony tumor lying in the hollow of the left foot which was not attached at any point to the bones of the foot. The patient's history is as follows:

Male, twenty-four years of age; occupation, car repairer. He gave an indefinite history of having had rheumatism of a mild grade on one or two occasions. Two years previously he noticed a small tumor about the size of a hazelnut lying toward the inner side of the plantar arch of the left foot. This was not movable or painful. The tumor had gradually increased in size until it completely filled the plantar arch of the foot. The patient's health remained good. He had never suffered any pain or inconvenience from the tumor except a slight tenderness when walking and the inconvenience of having the entire plantar arch filled up by the mass. He had not stopped work. The skin over the tumor was apparently normal, had never been reddened or sensitive, and the blood-vessels were not dilated. The entire mass felt smooth and firm. The motion at the ankle-joint was not interfered with.

The *x*-ray photograph showed the entire arch of the foot filled with a bony mass (Fig. 212). Its attachment to the bones of the foot could not be demonstrated, but from the position of the tumor it was thought to have originated from one of them.

At the operation an incision was made over the head of the first metatarsal along the inner side of the foot, extending to the os calcis, and the skin and plantar fascia were dissected back from

---

* Reprinted from "Surgery, Gynecology, and Obstetrics," July, 1912, pp. 119, 120

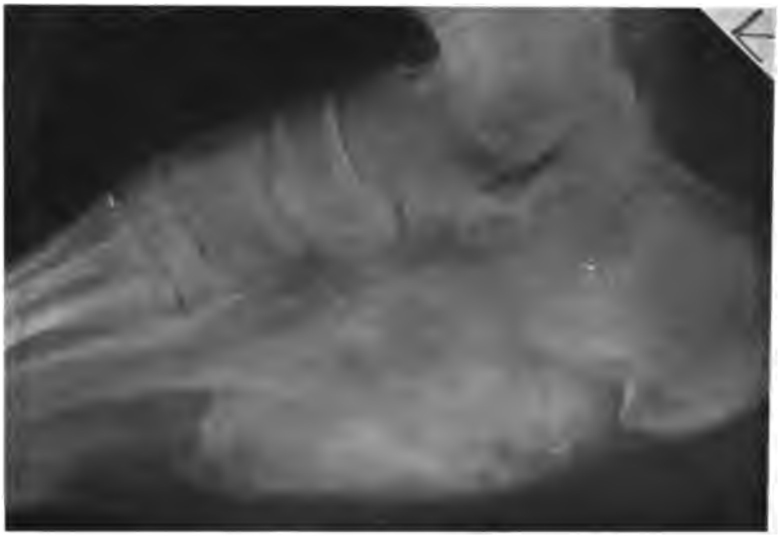


Fig. 212.—*X*-ray No. 12,388. Original radiogram. Region: left foot. Lateral view of plantar aspect. Note irregular outline bony tumor beneath plantar arch. At operation an encapsulated osteoma was found and removed. No bony attachment at any point.

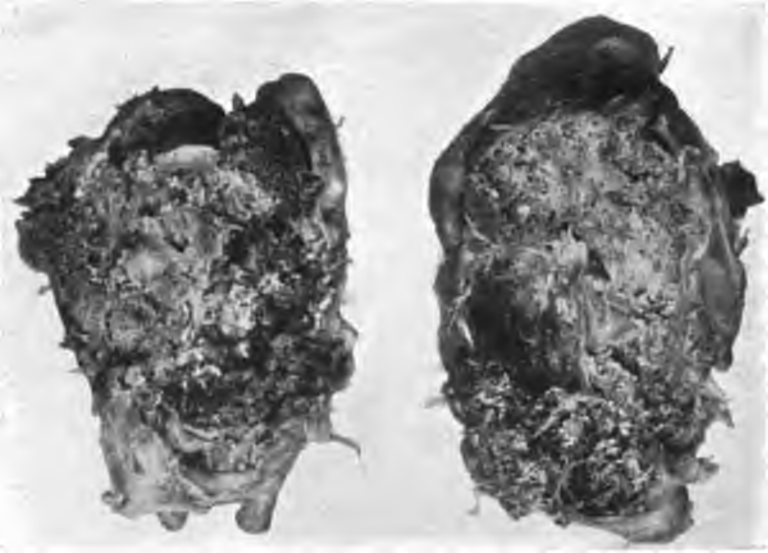


Fig. 213.—The two halves of the tumor after removal, showing the bony structure of the growth.

off this growth. The growth was then seen to be irregularly nodular, with many wart-like projections which had pushed through the fascia. On account of the size of the tumor, it could not be exposed, and it was split through the center with a chisel and half of it removed. After obtaining more room in this way, the other half of the tumor was enucleated intact, and was found to rest upon the deep tendons of the foot, but no bare bone was exposed at any point.

The tumor consisted of bone and cartilage covered with a thick fibrous capsule, which, upon microscopic examination, showed no periosteum. The tumor weighed 160 grams, was irregularly oval, and measured 12 x 7 x 5 cm. (See Fig. 213.)

From the fact that this tumor was not attached at any point to the bones of the foot, that is was lying outside of the tendons, and because it did not have a periosteum, we believed at first that it was a sesamoid bone which, for some unknown reason, began to hypertrophy.

Sesamoid bones are not uncommonly found in the sole of the foot. Gray's "Anatomy" states that two small sesamoid bones are found in the tendons of the flexor brevis pollicis opposite the metatarsophalangeal joint of the great toe, occasionally one in the metatarsophalangeal joint of the second toe, the little toe, and, still more rarely, the third and fourth toes. A sesamoid bone is often found in the tendon of the peroneus longus, where it glides through the groove in the cuboid bone; one in the tibialis posticus opposite the inner head of the astragalus, and that one appears late in life in the tendon of the tibialis anticus opposite the smooth facet of the internal cuneiform bone.

Microscopically, the structure of this tumor is cancellated bone containing several areas of cartilage. It does not differ from the structure of many other new osseous growths developing from bone. We have not been able to determine its origin.

TECHNIC

MANAGEMENT OF THE OPENING IN THE TRANSVERSE MESOCOLON IN COMPLETING THE OPERATION FOR POSTERIOR GASTROJEJUNOSTOMY*

WILLIAM J. MAYO

The opening made in the transverse mesocolon through which the stomach is brought out posteriorly in the operation of gastrojejunostomy was originally closed by fastening the torn margins with several sutures to the posterior wall of the stomach at some little distance (one-half to one inch) from the gastro-intestinal anastomosis. Later these sutures were omitted because they were thought to be unnecessary. In our experience the omission proved to be unfortunate, since in one case six feet of small intestine herniated through the opening into the lesser cavity of the peritoneum, and on the twelfth day a second operation was required for the relief of intestinal obstruction.

It has been advised by some authorities to suture the margins of the opening to the jejunum just beyond the gastro-intestinal anastomosis, and this plan is practised by a few careful surgeons, although several cases of obstruction have been reported as resulting from it. For some years† when performing this operation I have turned the margins of the opening underneath and sutured the peritoneum of the lower surface with three or four stitches to the suture line which unites the stomach and jejunum. This technic has proved very satisfactory in our cases. However, two cases in which a fat transverse mesocolon was sutured in this way caused secondary trouble because of adhesions forming in a collar-like mass around the stroma, and cure was not obtained in either case until a second operation was performed in which the margins of the transverse mesocolon were dissected free and united to the stomach at a distance of an inch from the suture line of the gastrojejunostomy.

---

* Reprinted from "Annals of Surgery," March, 1912, pp 398, 399.

† Mayo: "Annals of Surgery," November, 1905.

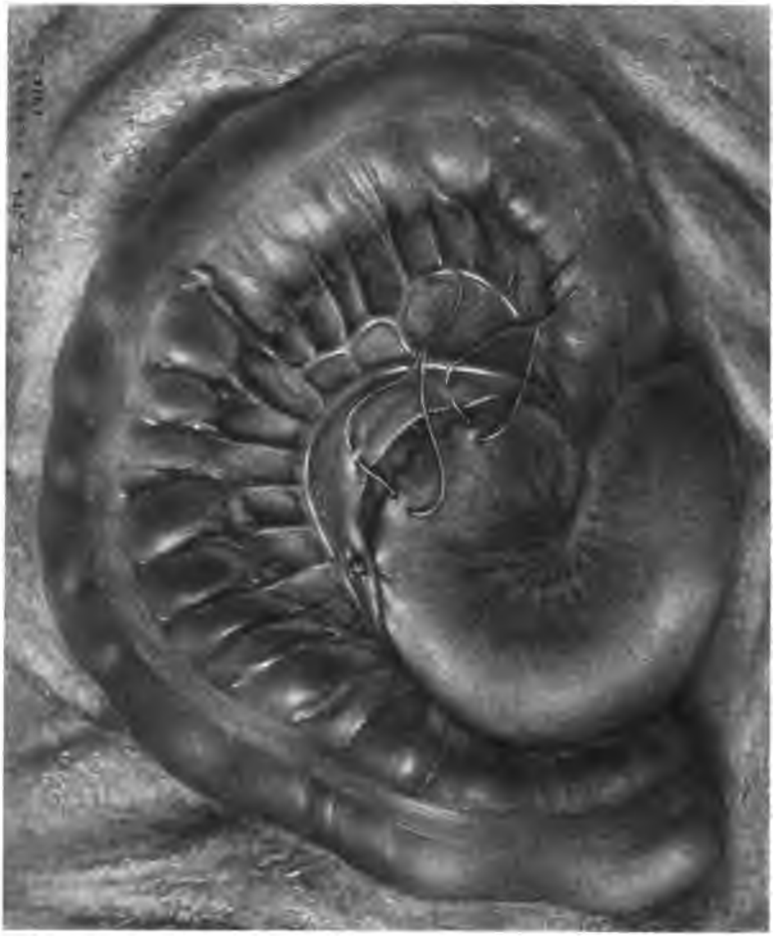


Fig. 214.—Thin transverse mesocolon sutured to the suture line in gastrojejunostomy.

Fastening the margins of the opening in the transverse mesocolon to the gastrojejunal suture line by several sutures and neatly tucking the edges underneath so there will be no raw surface to become adherent (Fig. 214) is an excellent practice and suitable in the large majority of cases. In the occasional case, however, in which the transverse mesocolon is quite fat, there is danger that adhesions will form, and this technic should not be adopted, but rather the old method of suturing to the posterior wall of the stomach three-fourths of an inch away from the gastro-intestinal anastomosing suture line (Fig. 215).

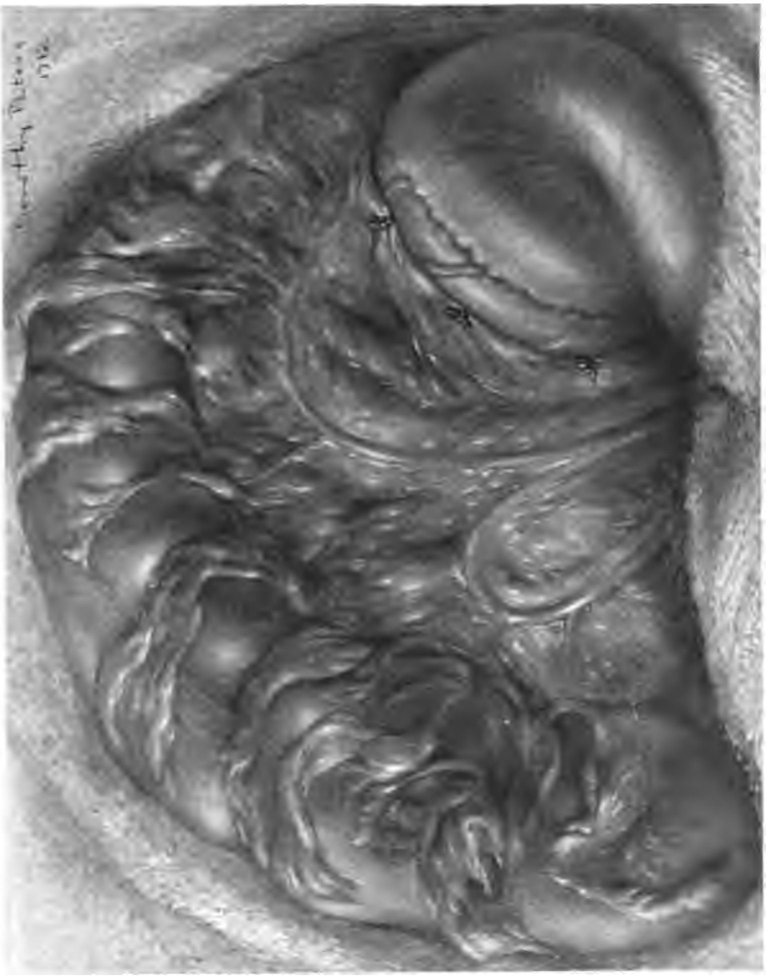


Fig. 215.—Fat transverse mesocolon sutured to the stomach.

NEPHRECTOMY WITHOUT DRAINAGE FOR TUBERCULOUS KIDNEY*

WILLIAM J. MAYO

Following nephrectomy for tuberculosis of the kidney it was formerly our practice to drain the cavity from which the kidney was removed, especially if tuberculous material had escaped into the wound. A sinus which was slow to heal often formed, particularly in the debilitated patient in whom the second kidney was somewhat involved. In many instances mixed infection with suppuration occurred, and undoubtedly was a contributing factor in the ultimate failure to cure the patient.

About two years ago a case of this type came under our observation. In operating, a large accumulation of whey-like fluid was found outside of the kidney, and, after removing the kidney, treating the ureter, and cleansing the wound as well as possible, the cavity, which held more than a quart, was filled with normal salt solution and the wound closed without drainage. The patient was greatly debilitated and had a moderate lesion of the remaining kidney. Primary union and a prompt and permanent recovery followed. The compensatory hypertrophy of the remaining kidney evidently furnished sufficient hyperemia to destroy such infection as may have existed within its substance. Since then, in operating on these cases, if the wound be soiled with tuberculous material, the cavity is cleansed as well as possible, filled with normal salt solution, and closed without drainage. I believe the normal salt solution enables material which is infected with tubercle bacilli in the attenuated state to be safely absorbed because diluted and absorbed quickly before there is an opportunity to establish favorable cultural conditions which would increase the virulence of the organisms. The normal salt solution is absorbed in the wound as rapidly as it would be if given in the usual manner subcutaneously.

---

* Reprinted from "Surgery, Gynecology, and Obstetrics," November, 1912, pp. 523, 524.

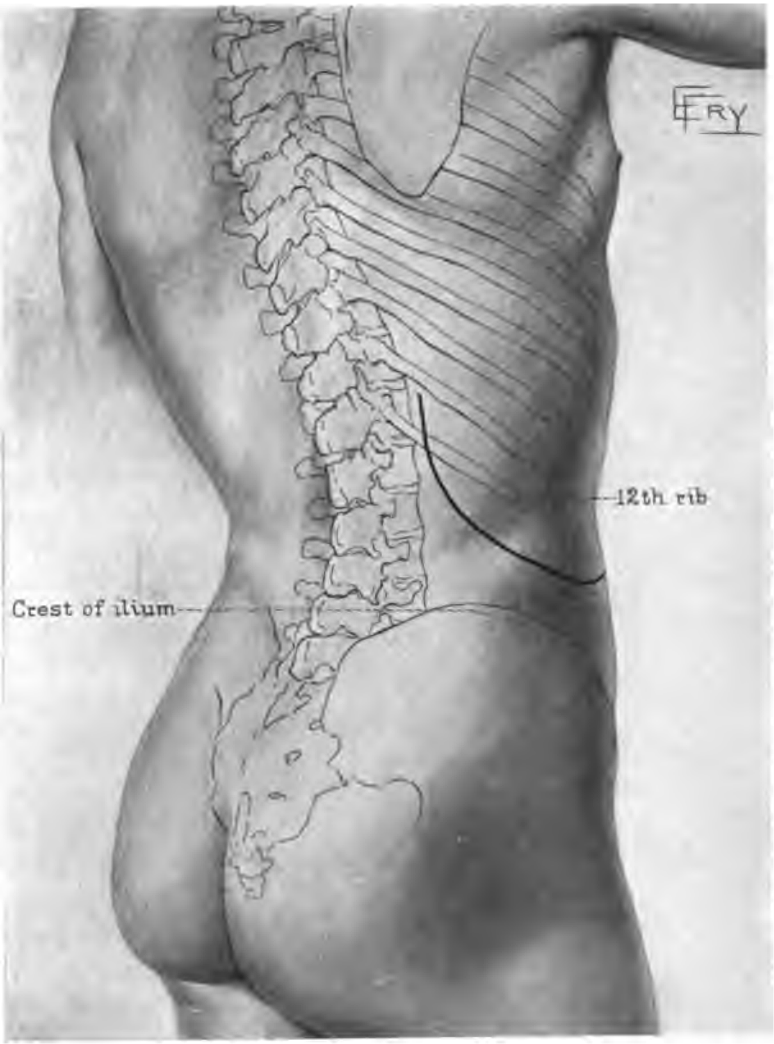


Fig. 216.—Incision for exposure of kidney.

In cases in which the tuberculous material has not escaped into the wound and the patient is otherwise in good condition, there is, of course, no necessity for using the salt solution, but drainage should not be employed.

Every effort should be made to remove the tuberculous kidney without the escape of its contents, and to secure this result an adequate incision is essential (Fig. 216). The patient is placed on the sound side with a considerable degree of elevation of the loin. A vertical cut frees the twelfth rib from its posterior attachments and a long transverse incision mobilizes the lower wall of the thorax. In this manner a large kidney can be removed with ease.

In some instances tuberculous material will have escaped spontaneously into the perirenal tissues before operation, and in such cases it will not be possible to remove the organ without distributing more or less of the tuberculous infection throughout the cavity of the wound. It is in these cases particularly that drainage has resulted so unfortunately and, I believe, has been an unnecessary procedure.

The stump of the ureter is a source of possible infection in the wound, and many surgeons either remove the kidney and ureter completely at the primary operation, or they suture the stump of the ureter to the skin for the protection of the wound.

For a number of years it has been our practice to inject 10 to 20 minims of phenol (liquid 95 per cent.) into the ureter. This distributed down through the lumen, and a ureter thus treated will rarely give trouble later.

I am convinced that in draining these cases we made a mixed infection possible which was responsible for many of the postoperative conditions we heretofore believed were inherent in the process itself.

Experience has taught us that drainage following operations for tuberculous lesions within the abdomen is unnecessary and usually followed by sinus and fistula; so also have we learned that draining the cavity from which a tuberculous kidney has been removed gives rise to complications which delay or prevent healing, and which may lead to the death of the patient some months later.

AN APPARATUS FOR THE INJECTION AND LAVAGE OF THE PELVES OF THE KIDNEYS AND THE URETERS*

G. J. THOMAS

In using a syringe or any other apparatus which has a pressure device to force fluid into the kidneys, there is always danger of renal overdistention and colic. In a few instances rupture of the kidney due to overdistention by the pressure method in cases of large hydronephrotic kidneys has occurred.

The frequency of overdistention and renal colic resulting from injecting the pelvis of the kidney and the ureters with shadow-casting fluids by means of a syringe suggested to me the idea of using an apparatus with only sufficient force of gravity to cause the flow to reach the kidneys.

In using the pressure method it is difficult to control the amount of pressure used, and the examiner cannot always stop the pressure in time to prevent overdistention. This error causes the patient great annoyance, and may cause intense pain for a number of hours following the examination. Moreover, in using the syringe we are not always able to withdraw the colloidal silver solution from the kidneys and ureters. By means of the apparatus described herein the pelvis of the kidney can be thoroughly drained of all the fluid which has been injected. This procedure is especially helpful in large hydronephroses and pyonephroses, when it is necessary to inject a large quantity of fluid into the kidney.

Description of Apparatus.—An ordinary small telescoping irrigating-stand with a cross-arm at the top of the telescoping rod

---

* Reprinted from "Jour. Amer. Med. Assoc.," submitted for publication November 8, 1912.

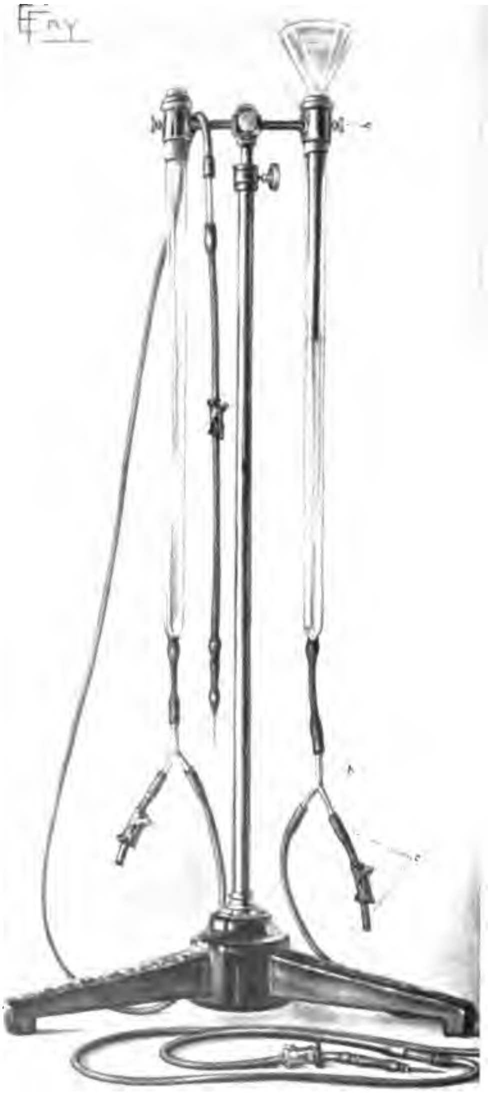


Fig. 217.—An apparatus for the injection and lavage of the pelves of the kidney and the ureters: *a*, Control screw for raising or lowering single buret; *b*, "Y" tube; *c*, tube for draining unused colloidal silver solution.

is used. The cross-arm is made to hold two 50 c.c. titrating burets. At the lower end of the buret is a short piece of rubber tubing of small caliber, which is connected to a "Y"-shaped glass tube. To one arm of the "Y" 4 to 5 feet of pressure tubing is attached, and to this tubing is attached the needle which is inserted into the lumen of the catheter. To the other arm of the "Y" is attached 3 to 4 inches of rubber tubing, which has a stop-cock at its end. This is used to drain the colloidal silver from the buret before beginning to siphon. In this way the fluid which has not been used can be saved. Water may be poured into the burets to replace the colloidal silver before beginning to siphon. The control screw is used to obtain different heights of the tubes.

We have used this apparatus in more than 50 injections, and in only one case did colic occur. This was in a case of stone in the ureter, and the catheter became plugged after passing the stone. There was a large hydro-ureter with hydronephrosis above the stone, and, since the backed-up urine could not drain off, the colloidal silver suddenly cleared the catheter and caused the temporary pain of overdistention. This was quickly relieved by lowering the instrument below the level of the patient and siphoning off some of the retained secretion.

In most of the cases which have been injected no measured amount has been used, because there is so little pressure that the colloidal silver will outline the pelvis or the ureter and return around the catheter without causing overdistention.

The pyelogram is taken while the fluid is being injected, and the pelvis or the ureter is kept as full as possible at the time the exposure is being made. The instrument works mechanically and the examiner is not exposed to the *x*-ray while using this method.

The apparatus has been used in cases of double pyelitis when it has been necessary to lavage the pelves. Both pelves can be washed at one time, and the fluid is allowed to run slowly until the patient complains of irritability of the bladder. In this manner irrigation may be continued for a longer period without causing pain.

Only the force of gravity is depended upon to cause the flow into the kidneys, the tubes being raised only far enough above the level of the patient to overcome the resistance of tubes and catheters. After allowing a few cubic centimeters of the colloidal silver to run in, the pyelogram is taken while the solution is still running, and after this has been completed, the tubes should be lowered at once below the level of the patient, and the colloidal silver siphoned out.

The improvements in technic which we have noted in using this method of injecting the pelves of the kidneys and the ureters are—(1) Distention of the pelves of the kidney or ureter, or both, without causing colic; (2) a pyelograph can be taken while the pelvis is under the pressure of constantly running fluid, and without exposing the examiner to the *x*-ray; (3) colloidal silver or other solutions can be siphoned off quickly after the plate has been made; and (4) it is useful in slow and prolonged lavage of both renal pelves.

The instrument shown in the drawing is a modified Boehm salvarsan apparatus. An instrument used to inject the kidney should be larger than the Boehm apparatus, so that it can rest on the floor and be raised to a height of six feet.

AN OPERATING-ROOM MIRROR*

A DEVICE TO FACILITATE THE VIEW OF OPERATIONS IN THE OPERATING THEATER

DONALD C. BALFOUR

It is an appreciated fact that in operating in amphitheaters and clinic rooms, many of the exact details of an operation are lost to the observer who is not in an advantageous position. This is due chiefly to two reasons: first, the angle from which the observer views the operation does not give the true relationship of the structures; second, his view is often totally obstructed by either the surgeon or the assistants.

To overcome this difficulty, different devices, chiefly in the form of mirrors, are in use in various clinics in England, Scotland, and on the continent, but so far as is known they have not been tried in this country.

Based on this idea, a mirror was constructed for the Mayo Clinic, and it has been used long enough to demonstrate its usefulness and warrant a brief description. Granting that the rather small operating rooms in this clinic are more suitable for successful application of such a device, yet its modification would be practical for use in rooms of larger size.

The mirror is rectangular in shape and measures 62 inches by 32 inches. It is suspended from the ceiling by two rods, one at the center of each end, and any angle is readily obtained, as the attachments of the rods are hinged and can be fixed in position by the screws. The mirror is suspended at a height at least 6 feet above the operating table, which is placed immediately beneath, with its

---

* Reprinted from "Annals of Surgery," September, 1912, p. 454.

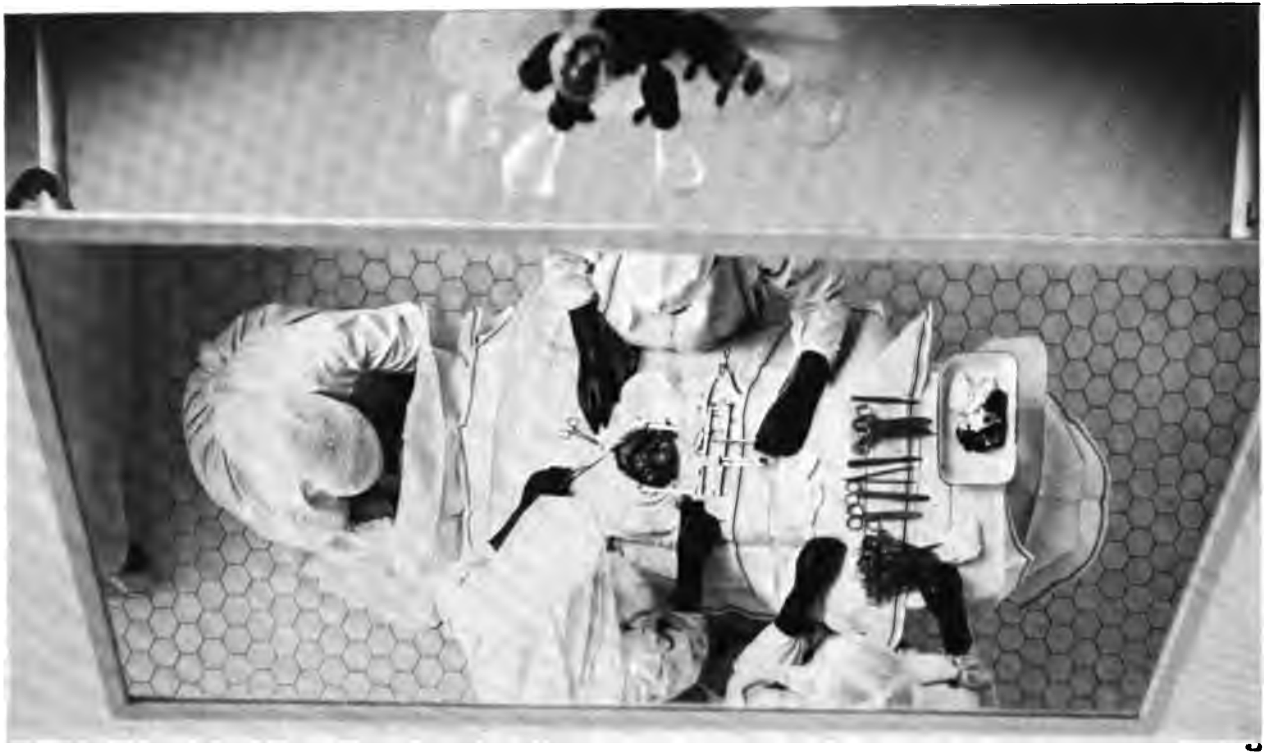


Fig. 218.—Photograph of operation as reflected in mirror above operating table.

length parallel to the long axis of the mirror. The angle of the mirror is adjusted so that the observer, looking in the mirror, obtains a view of the operative field, as shown in Fig. 218. This arrangement gives the spectator a true image of the operative field, the only disadvantage being that one must become accustomed to the novelty due to the impression that the operator and assistants are left-handed.

A SIMPLIFIED TECHNIC FOR THE APPLICATION OF THE GLYCYLTRYPTOPHAN TEST TO GASTRIC CONTENTS*

FRANK SMITHIES

For those who desire to make routine observations on the presence of peptid hydrolyzing enzymes in stomach extracts (particularly in cases of carcinoma ventriculi), the procedure here described may prove of value. It has been employed in the laboratory of gastro-enterology at the Mayo Clinic in more than 800 cases. The results have been as dependable as with the original "glycyltryptophan test" described by Neubauer and Fischer.†

Glycyltryptophan Test

The preparation of this dipeptid, regularly sent out by Kalle and Company (Biebrich am Rhein), under the direction of Neubauer and Fischer, consists of practically 1 c.c. of a glycyltryptophan solution, under about two times its volume of toluol. This is contained in a thick-walled, glass-stoppered bottle. The body of the bottle is marked, just below its neck, to indicate to what extent the volume of contained glycyltryptophan solution is to be diluted with filtered gastric extract. Examination of the bottle's capacity demonstrates that the proportion of glycyltryptophan and gastric extract, when the test is set up, is approximately as one to ten. Carried out in this manner, each test costs about 65 cents.

Inquiry showed it possible to obtain a solution of the glycyltryptophan under toluol from Kalle and Company in bottles holding from 10 to 150 c.c. Accordingly, we have been accustomed to obtain the dipeptid in bulk in this manner.

---

* Reprinted from "Jour. Amer. Med. Assoc.," April 6, 1912, vol. lxiii, pp. 1008, 1009.

† Neubauer and Fischer: "Deut. Arch. f. klin. Med.," 1909, vol. xcvii, p. 499.

The test is set up as follows:

1. Test-tubes of 10 c.c. capacity are employed. These should be carefully cleaned with boiling water and dried inside. They are numerically marked for identification with a wax pencil. Into each test-tube is carefully measured, by means of a sterile graduated pipet, 0.5 c.c. of the glycyltryptophan solution. (Closing the proximal end of the pipet with a finger allows the pointed distal end to pass through the toluol layer overlying the glycyltryptophan solution, and the dipeptid to be withdrawn with the minimum of contamination.) Five c.c. of the recently secured filtered gastric extract are then measured by a clean, graduated pipet, and poured into the correspondingly numbered test-tubes, to which glycyltryptophan solution has been already added. Two control tubes are used. In one are placed 0.5 c.c. of glycyltryptophan solution and 5 c.c. of normal salt solution and into the other is placed 5 c.c. of normal salt solution, without added glycyltryptophan solution. In the entire series, each tube next receives 0.5 c.c. of toluol (toluene, Merck). The contents of the tubes are then mixed by inverting several times. The tubes are next placed in a water-bath (an incubator may be used) at 37° C. for twenty-four hours.

2. At the expiration of the incubation period the test-tubes are removed from the water-bath. Clean test-tubes of 10 c.c capacity and numbered to correspond with the gastric extracts tested, as well as the controls, are set in racks. Into each of these tubes is measured, by means of a graduated pipet, 2 c.c. of the glycyltryptophan-gastric-extract mixture lying below the toluol in the recently incubated tubes. To each tube are then added three drops of a 3 per cent. glacial acetic acid in distilled water solution. The tubes are well shaken. Bromin vapor is allowed to flow into each tube, until it appears amber yellow above the contained fluid. The tubes are again shaken. Examination by daylight (preferred) or by white, artificial light is now made for evidences of the characteristic rose-pink reaction between the amino-acid (tryptophan) and the bromin.

TRYPTOPHAN TEST

As suggested by Weinstein,* this is made, as routine, on the fresh gastric extracts, inasmuch as occasionally swallowed saliva, amino-acids, regurgitated duodenal contents, and the like may give the bromin vapor reaction, before incubation or without the addition of a dipeptid such as glycyltryptophan. Five c.c. of each fresh, filtered gastric extract is poured into test-tubes of 10 c.c. capacity, acidulated with the 3 per cent. acetic acid solution, and treated with bromin vapor as above. If no characteristic rose-pink color results, the tubes are incubated with the corresponding specimens that have been mixed with glycyltryptophan solution. For accurate work, it has seemed best to us to cover these "tryptophan test" contents with a layer of toluol. At the end of twelve, twenty-four, and forty-eight hours note is made of changes in color, and these results are compared with those obtained with the preparations in the first series.

Advantages of the modification:

1. The expense of the test is reduced to one-tenth of the commercially marketed, sealed bottle method. This is a considerable saving when hundreds of tests are made as routine, or when frequent tests are made in a given case.

2. Interpretation of color changes in the thick-walled glass bottles is often difficult. Slight changes in color are readily distinguished in the small, thin glass test-tubes.

3. Breakage is not infrequent when the thick-walled, sealed bottles are used. This means another test-bottle or a questionable result.

4. Occasionally 10 c.c. of filtrate, as required by the bottle method, cannot be obtained. If less be used, the extract may not contain sufficient enzyme to hydrolyze the glycyltryptophan.

---

* Weinstein: "Jour. Amer. Med. Assoc.," October 28, 1911, p. 1420.

A METHOD FOR THE MICROSCOPIC EXAMINATION OF GASTRIC EXTRACTS AND OF FECES*

FRANK SMITHIES

Smears of gastric extracts or of emulsions of feces, as ordinarily made, generally return partial or unsatisfactory findings. This is apt to be so when specimens are examined with an oil-immersion objective. In an effort to make of greater worth the routine microscopic examination of gastric extracts particularly, the procedure described below has recently been adopted at the laboratory of gastro-enterology of Mayo Clinic.

Advantage is taken of the opportunities offered by agar solutions recently emphasized by Ross.† These may be combined with anilin dyes and chemicals to suit the work in hand.

Agar Solutions.—Two per cent. agar solution is made by boiling an appropriate quantity of best grade strip agar in distilled water. The solution is filtered several times while very hot through double, hydrochloric-acid-washed filter-paper. On cooling it solidifies as a firm jelly. It should be fractionally sterilized and refiltered on three consecutive days.

For purposes of convenience, 5 c.c. of the molten agar are poured into each of numerous sterile test-tubes. The tubes are plugged with sterile cotton and set aside at room temperature. The agar jellies and may be used as desired.

Stains.—Thus far we have used coloring agents in combination with agar solutions for two purposes: (1) For the differentiation of bacteria, blood-cells, epithelial elements, tissue-bits, and the like, we have employed Unna's polychrome methylene-blue, Gram's mixture, hematoxylin, thionin, methylene-blue (Löffler's), and Wright's stain; (2) for the differentiation of starch residues, vegetable fibers, molds, etc., we have employed freshly prepared Lugol's mixture.

---

* Manuscript submitted for publication March 29, 1912. Reprinted from the "Archives of Internal Medicine," June, 1912, vol. ix, pp. 736–738.

† Ross, H. C.: "Induced Cell Reproduction and Cancer," Philadelphia, 1911.

Procedure.—For each specimen of gastric extract or feces emulsion we make two agar-coloring matter combinations as follows: The 2 per cent. agar jelly is liquefied by heating over a Bunsen flame. Two cubic centimeters of the solution are poured into each of two small test-tubes (those measuring 10 cm. x 15 mm. answer very well). Into each of the tubes are then poured 15 drops of filtered staining agent. For staining bacteria and the like we have found that Unna's mixture gives good results, while Lugol's solution colors starch elements better than simple iodin. The added stains are intimately mixed with the agar and the tubes promptly placed in a beaker containing boiling water. The agar is thus kept as a solution.

Very thin smears of the gastric extracts or feces emulsions are made on cover-slips. It is desirable to avoid getting gross particles of food in the smears. The smears may be dried in air or by rapidly passing through a gas-flame.

Onto the smear to be examined for microörganisms and allied elements, by means of a pipet with a 1 millimeter bore, is placed 1 drop of the agar-methylene-blue mixture. The cover-slip is promptly inverted on a clean glass slide. The agar-stain mixture rapidly spreads to the edges of the cover-slip. As it cools the agar solidifies, while the stain mixed with it permeates the smear. Similarly, to the smear to be examined for starch remnants and the like is added 1 drop of the agar-Lugol's mixture. The cover-slip is mounted at once on the same slide as the first preparation. About two minutes suffice for firmly mounting and staining ordinary material. In a series, the first preparations are ready for examination by the time the last are made.

Examination.—The preparations are best examined by such light as comes from a Nernst, Schwann, or tungsten lamp. If electricity is not available, a Welsbach mantle light suffices.

When the specimens are properly focused, using an oil-immersion objective, it will be seen that bacteria are stained blue or deep purple (Unna's mixture); blood-cells and nuclei are differentiated by pale pink and blue, as are also epithelial elements; tissue bits, if small, may show atypical mitotic cells; muscle-fibers are pink to red, with deeper striation; mucus is in bluish strips or whorls. Unless the preparation is overstained, vegetable fibers, leptothrix, molds, etc., are but lightly colored. In the smear prepared with agar-Lugol's mixture vegetable fibers, leptothrix, molds, and starch remnants are appropriately differentiated. The latter may be amethyst-blue, with deeper staining centers or laminæ, reddish-pink, with mahogany-colored centers, or faint pink or colorless. Budding yeasts, molds, and occasionally bacteria take a brownish-blue tinge. Vegetable cells stand out prominently as blue to brown reticulum. Large masses of amorphous material stain variously, but are readily distinguished from microörganisms.

Uncolored Preparations.—The agar without coloring agents added may be advantageously used for mounting smears. In fresh preparations, when the smears are not dried, motile organisms (bacteria, protozoa) may be observed for a long time. This is facilitated when the specimen is diluted with three volumes of warm normal saline solution before the smears are made.

ADVANTAGES OF THE METHOD

A routine, differential report on two dozen smears, from half as many specimens of gastric extracts or feces, may be made in about thirty minutes. The specimens are simultaneously mounted and stained. The solidification of the agar gives so firm a mount that the specimens may be examined with high or low power, with the stage of the microscope at any angle. The mounting is sufficiently permanent to allow future study (we have preparations showing good fields after ten weeks), drawings, photomicrographs, or demonstration. Comparison of the smears on the same slide, but differently stained, results in many interesting and instructive observations. There would seem to be advantages in using the method for the observation of motile bacteria, protozoa, or cells with ameboid activity, when uncolored agar solutions are used.

GENERAL PAPERS

GRAFTING AND TRAUMATIC DISSEMINATION OF CARCINOMA IN THE COURSE OF OPERATIONS FOR MALIGNANT DISEASE*

WILLIAM J. MAYO

Autogenous grafting of carcinoma may occur spontaneously, especially at points of contact, as about the labia, vulva, and in the gastro-intestinal tract. In the large intestine, at least, grafting may occur not only at points where the mucosa of the opposite wall of the intestine comes in contact with the carcinoma, but has been known to occur by the process of "seeding," in which malignant cells from the tumor have become detached and grafted on the surface of the mucous membrane, sometimes at a considerable distance from and usually below the original growth. The grafting may take place above the growth as well, the cells being carried to proximal points by antiperistalsis.

In the days of Rokitansky and Virchow, morbid anatomists recognized autogenous grafting of carcinoma, and interesting references to its occurrence will be found in the literature of that period. However, very little seems to have been written concerning it within recent years. I remember an incident which occurred while I was a student in medicine: my father called my attention to a carcinoma of the upper lip which had grafted from an advanced carcinoma of the lower lip, and told me that he had observed similar conditions in other situations.

Realizing the possibility of spontaneous autogenous grafting of carcinoma, we must also appreciate that the condition may be induced by operative manipulations.

---

* Reprinted from "Jour. Amer. Med. Assoc.," February 15, 1913, vol. lx, pp. 512, 513.

In one of our early resections of the pyloric end of the stomach an unpleasant experience occurred. The abdominal wall became infected with carcinoma in the needle punctures made in closing the abdominal incision. This was before the days of elastic clamps which control the escape of the carcinomatous material into the abdominal wound. After this example of carcinomatous grafting we began searing the raw surfaces of the stomach and duodenal stumps following partial gastrectomy for cancer, because we believe that grafting sometimes occurred from bits of loosened carcinomatous tissue freed at operation and left in the cavity of the stomach.

Autogenous peritoneal grafting in carcinoma of the stomach occurs frequently, and is especially common in Douglas' pouch. These points of grafting may be felt by rectal examination as typical nodules attached to the anterior wall of the rectum on its peritoneal surface. The ovaries are particularly susceptible to such grafting; the involved organs rapidly become cystic, and may obscure the original focus of the disease. An example of late grafting occurred recently in our clinic. The patient, a woman aged thirty-eight, from whom two-thirds of the stomach had been removed two and one-half years previously, returned to the hospital with secondary involvement of the ovaries and pelvic peritoneum, but without evidence of involvement in the upper abdomen. Another case which occurred in our experience is an example of the possibilities of carcinomatous grafting in a granulating wound. A two-stage operation for carcinoma of the rectum was performed. At the first operation a permanent colostomy was made in the left rectus muscle, and after thoroughly cleansing the rectum and lower sigmoid by means of irrigation between the anus and colostomy wound, on the twelfth day the entire rectum and rectosigmoid were removed from behind, using a modified Kraske exposure. The sigmoid was divided at a point six inches above the growth, the end turned in and left as a blind attachment to the colostomy wound. The patient made a prompt recovery and went home at the end of four weeks. Seven weeks later he returned with a typical carcinomatous growth on the inner edge of the colostomy opening. At the time of his dismissal from the clinic there was a small granulating area unhealed on the mucocutaneous margin of the colostomy wound. There were no other evidences of metastasis, and after the removal of the localized growth the patient had no further trouble (Fig. 219). The obvious explanation in this case is that, during operative manipulations, pieces of the carcinoma were loosened and left in the sigmoidal pouch, and as they were discharged out of the colostomy opening, grafting took place at the site of the granulations, just as bits of skin might have been grafted to this surface.

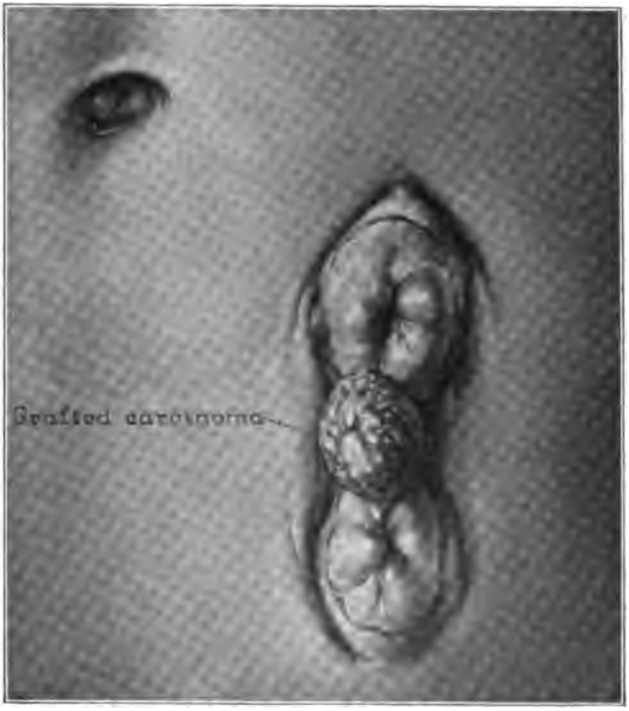


Fig. 219.—Carcinoma grafted on granulating left rectus colostomy wound.

Therapeutic grafting of normal epithelial elements to cover raw surfaces is, of course, a well-known procedure. The Reverdin grafts and the Thiersch and Wolf grafts represent the common forms. That therapeutic grafting is by no means confined to autogenous sources is shown by the excellent work of Davis,* who has grafted such surfaces by means of cold storage material obtained from amputated limbs, etc., and uses it successfully as long as four weeks after the amputation. We know that epithelial cancer has potential initiative far in advance of normal epithelium, and that which happens under scientific direction for therapeutic purposes may be equaled by pathologic accident.

One reason for the small percentage of permanent cures following operations for cancer of the cervix is the proximity of the ureters to the cancerous process in the cervix. Normally, ureters and cervix are three-fourths of an inch apart, but with malignant involvement of the cervix they lie in contact. While it is true that the ureters are not often involved primarily, we cannot expect to push them back out of the way during operative manipulations without carrying infection, as the results often demonstrate.

Traumatic dissemination of malignant disease is not uncommon. We have observed several cases of cancer of the breast which have been squeezed and manipulated by ignorant persons until a comparatively curable case has been rendered hopeless because of acute involvement of the skin and fascia.

Embolic vascular dissemination through traumatism is common, especially in cancer of the rectum. The infected thrombi in the derivatives of the portal vein are loosened and are carried to the liver.

It is now nearly fifteen years since we abandoned cutting instruments for the cautery knife in performing vaginal hysterectomy for cancer of the cervix. We believed that vaginal hysterectomy done in this way furnished an opportunity for carcinomatous infection of the wound and traumatic dissemination through the lymphatic and vascular systems. It is worthy of note that while we had few cures during the period in which the knife was used, we noted a very considerable percentage of cures after adopting the use of the cautery. The unexcelled results achieved by Byrnes in the use of the galvanocautery in high amputations of the cervix for carcinoma were probably due largely to the elimination of these causes of cancer dissemination.

---

* Davis: "Annals of Surgery," 1910, vol. li, pp. 40–51.

The better results attributed to abdominal hysterectomy for cancer of the cervix as contrasted with vaginal hysterectomy may not be due so much to the removal of the pelvic and iliac lymphatic glands as to the fact that thorough destruction of the carcinomatous cervix is accomplished with the cautery immediately preceding the abdominal incision. When such thorough destruction has been made immediately preceding vaginal hysterectomy, we have observed very little if any difference in the ultimate results, other things being equal. There are, however, as large number of cases not suitable for the vaginal operation, and in which the abdominal route, by furnishing freer access, gives better results.

The removal of pieces of tumor for microscopic examination should be attended by some precautions, and, if possible, preparation for the immediate extirpation of the growth should be made if the frozen section shows malignant disease. If the suspicious tumor be localized, as in the breast, it is wise to remove the entire tumor for examination without cutting into it, and then, if necessary, do the radical operation at once. If removal of the specimen cannot be followed by immediate extirpation, the wound in the growth should be sealed by the use of the actual cautery or pure phenol.

We should take into strict consideration the possibility of the dissemination of carcinomatous material during operative procedures. A specialized technic should be inaugurated in which carcinomatous processes would be treated as though they were the focus of virulent infection.

The first and most important principle in operations for malignant growths is wide local extirpation. More than a quarter of a century ago Heidenhain established the law that in operating for the removal of carcinomatous growths the limiting incision should be made at least 3 cm. from the visible expression of the disease. This limit is now considered by surgeons to be altogether too narrow for safety.

The second principle is the removal of the tributary lymphatics, if possible by block dissection, as advocated by Crile. In this procedure the lymphatic channels, glands, and the primary disease are removed in one mass.

The third principle in the operative technic in these cases is to avoid grafting or traumatic dissemination of malignant cells during the course of operation, and by proper prophylaxis prevent the possibility of grafting following operation.

CONTRIBUTIONS OF THE NINETEENTH CENTURY TO A LIVING PATHOLOGY*

WILLIAM J. MAYO

I wish to thank the trustees of the Massachusetts General Hospital for the high honor conferred in asking me to deliver the Ether Day address for 1912, an honor which is emphasized by the eminence of the men who have preceded me in addressing you on previous occasions.

The nineteenth century introduced methods of investigation which made the practice of medicine one of the sciences. Previous to this time clinical observation, with all its vagaries, had constituted the basis of medical practice. Anatomy, physiology, chemistry, and pathology had been studied and valuable material obtained, but as yet no sound theories had been advanced from which deductions applicable to the treatment of disease could be made.

The figure presented to my mind as the dominant one of the eighteenth century is that of John Hunter. Hunter was anatomist, physiologist, and pathologist, and the great surgical philosopher of his time. His vision was prophetic, and he employed methods of experimental research which are a model for this day. Jenner introduced immunity by vaccination, and in presenting his subject said that he thought certain hypotheses to be correct. Hunter wrote to Jenner and said, "Why think? Try it on a hedgehog and know." Hunter persistently and conscientiously studied the gross manifestations of disease so far as they could be studied by the unaided eye, and as a result of his work macroscopic pathology became definitely established. He made classifications and arrangements of findings in gross pathology, especially as related to surgery. These specimens were secured largely from investigations made at postmortems, and, because of them, pathology was taught, not as before, from the standpoint of clinical observation, but from the actual material taken from the diseased body. I believe it to be the duty of every surgeon who can do so to make a pilgrimage to the Royal College of Surgeons of England for the purpose of seeing the hundreds of specimens labeled in black with Hunter's own hand. Hunter's preservation of these carefully recorded specimens saved for teaching purposes was instrumental in establishing a school which made England the center of research in the field of scientific medicine, and this work resulted in an enormous impetus to scientific investigation the world over.

---

* Address delivered at the Massachusetts General Hospital on the sixty-sixth anniversary of Ether Day, October 16, 1912. Reprinted from the "Boston Med. and Surg. Jour.," November 28, 1912, vol. clxvii, pp. 751–754.

Pathology is the foundation of scientific medicine. Without a correct understanding of the nature of disease the practice of medicine as a science would not be possible.

For the purpose of this discussion pathology will be divided into two parts: First, a pathology representing terminal conditions, and which, for want of a better name, we will term "postmortem" pathology; and second, the pathology which deals with disease in the living when the condition is still curable, and which we will call "living" pathology.

Postmortem pathology furnishes valuable data for teaching purposes, because it is obtained from advanced processes which best represent the characteristics of the condition and adds greatly to the science of medicine. Unfortunately, from a therapeutic standpoint, the data are obtained too late to make restoration to the normal possible.

Living pathology deals with disease during the period in which a restoration to the normal or physiologic condition can be brought about by appropriate therapeutic measures, and to this end the art of medicine is directed.

In studying the nature of disease, as exhibited by the terminal pathologic findings, an intense desire was inspired to deal with these processes in the early and curable stage. As a means to this end anatomy, especially regional anatomy, became the subject of more accurate study. France led in this field of work, bringing anatomy to a high stage of development, and with it a specialized surgical technic, thus in her turn becoming the great medical center of the civilized world.

In those early days operations were fraught with terrible suffering to the patient. They were undertaken only under dire necessity, and scientific method was sacrificed to speedy manipulation. The speed with which some of these old-time surgeons worked was phenomenal, major operations being performed in two minutes.

The knowledge acquired concerning gross pathology and gross anatomy introduced a great necessity out of which developed the priceless boon to humanity—anesthesia. Influenced and aided by this discovery, surgeons could now operate upon pathologic processes in the early stages, and the art of surgery developed rapidly.

Although operations were performed upon the surfaces of the body and the extremities, the cavities of the body containing the important organs remained as a closed book to the surgeon. The pathologic changes found within the cranium, thorax, and abdomen at postmortem seemed to indicate that surgery could not be developed to an extent which would enable the adoption of remedial measures.

Because of certain uncontrollable conditions with which surgery was surrounded in the early days, the mortality which followed directly upon even minor operations was appalling. Then came Pasteur, who, like Hunter, brought the sense of sight, but aided by the microscope, into the field of science. The discovery of the germ origin of disease made Pasteur the greatest benefactor the world has ever known. The only name in science which ranks with Pasteur is that of Darwin, whose discoveries revolutionized the natural sciences and had a most profound influence upon scientific medicine. Virchow's splendid work had placed cellular pathology upon a sound footing, preparing the way to a prompt recognition of the rôle of bacterial agents in the production of disease. In Germany especially was the relation of the germ theory to the origin of disease studied zealously, and many of the discoveries which reconstructed the foundation of medicine were the result. Germany thus in her turn became the center of the medical sciences.

With Pasteur's name must be associated that of Lister. The theory of the germ origin of disease suggested to Lister the explanation of certain phenomena in which he was greatly interested. Investigations followed which developed the crowning triumph of modern surgery,—antisepsis,—and led to the final achievement—asepsis. Lister showed the application of the germ theory to the treatment of wounds, and under his teaching operative procedures became comparatively safe.

The prevailing views concerning the pathology of the organs in the cavities of the body were not sound. Clinical observations gave rise to conflicting opinions, and many symptom-complexes were supposed to be pathologic entities. Attempts to clear up the confusion by postmortem observations were not successful, because autopsy did not disclose the condition as it existed during life, but rather the particular lesion which caused the death of the patient. In acute conditions this information was, of course, valuable, but in chronic conditions it often added to the confusion and gave rise to theories which later proved untenable. It is a true saying that "Few die from the disease with which they suffer during life." A few years ago no fact in pathology was considered indisputable unless derived from the postmortem, and this attitude of the medical profession was responsible for much of the pessimism directed toward therapeutics.

A series of studies made by various investigators on terminal infections revealed the nature of the processes which cause death and produce many of the conditions found at postmortem—conditions which were previously believed to be a part of the original lesion instead of a sequence to it.

Anesthesia and asepsis enabled surgery to assume an important part in solving the discrepancies between postmortem findings and the nature of the disease as it existed during life. Surgery was positive and active, and one organ after another became the object of this form of study during life. Though not always successful from a therapeutic standpoint, surgical investigation did not fail to yield new truths to the science of pathology. In this manner our views concerning diseased conditions in parts previously concealed from the sense of sight were greatly advanced.

The abdomen was a locality well suited to surgical investigation, and surgical procedures had become so safe that this great cavity could be opened and explored at a time when the disease was in a curable stage, before secondary complications obscured the real nature of the malady.

Tait was the pioneer in abdominal surgery. He was a general surgeon who had become interested in the special branch of gynecology. This specialty at that time was largely concerned in the local treatment of diseased conditions and minor operations. It had some real triumphs to its credit in the removal, through the abdomen, of certain large tumors of pelvic origin. In general, however, the views upon the nature of diseased conditions in the pelvis of women were notably incorrect. Extra-uterine pregnancy was believed to be a broad-ligament hematocele. Pelvic infections of tubal origin were supposed to be pelvic cellulitis. The Fallopian tube directly connects the outside of the body with the peritoneal cavity; various defenses exist to protect this portal against the invasion of bacterial agents, but they are often inefficient, and pelvic infection results. Tait opened the abdomen and demonstrated the exact nature of these debated conditions. He attacked these problems with vigor and greatly advanced our knowledge of pelvic pathology. Tait was a brilliant but eccentric man. Dogmatic in statement, his debates were characterized by an intolerance for the opinions of others which created much ill feeling in the profession against him, but his contributions to the living pathology of the abdomen were greater than those of any surgeon of his generation. His later years were made unhappy by hasty and ill-considered statements in regard to vivisection.

The greatest original contributions to our knowledge of infections in the abdominal cavity came from a physician and pathologist. Before Fitz made known to the world the part played by the appendix in the causation of these infections, many supposed diseases in the abdomen were named and described. The most common pseudonym was "inflammation of the bowels." The appendix in both sexes, like the Fallopian tubes in women, is a weak link in nature's chain of defense, and when diseased is capable of causing various manifestations from dyspepsia to a fatal peritonitis. Fitz made further important original contributions to the subject of intestinal diverticula, and especially to the infections of the pancreas.

A third weak point in nature's defense is the gall-bladder, and infections from this source are exceedingly common and vary from the colic of gall-stones to fatal involvement of the liver and pancreas. Knowledge in regard to disease of the Fallopian tube, the appendix, and the gall-bladder is common property, and deaths from these causes are now as rare as they were formerly common.

In spite of all research we do not as yet know the essential cause in the production of malignant disease, but that chronic irritation is a factor in the causation of carcinoma cannot be denied. Cancer is found in all vertebrate animals, and always in a situation in which the habits of the animal cause an irritation of the parts affected. We have recognized the fact that precancerous lesions due to chronic irritation occurred in organs like the skin, which are open to direct inspection, and based on this fact, irritated warts, moles, scars, etc., have been promptly removed. We seem, however, to have overlooked the fact that a like precancerous condition might exist in the internal organs. When modern methods of investigation brought the real facts to light, it was shown that chronic irritation of the internal mucous surfaces is as important in the development of cancer as it is on the cutaneous surface.

Cancer of the stomach, which comprises 30 per cent. of the total number of cancers occurring in the human body, was formerly known only from its postmortem characteristics, and the prognosis was wholly unfavorable. The demonstration of its living pathology has shown that it frequently arises in points of chronic irritation which are themselves capable of relief, thereby removing from the stomach the cause of a serious disability, distress, and malnutrition, as well as removing a cancer menace. Instead of the hopeless condition known to postmortem pathology, cancer of the stomach is today curable in a considerable percentage of cases.

Cancer of the gall-bladder is seldom seen without gall-stone irritation. It is found in about 4 per cent. of those cases which come to operation for disease of the gall-bladder. The danger attending an operation for gall-stones in the early stage does not exceed one-half of 1 per cent. The patient with irritating gall-stones appears to have 8 times the possibility of death from cancer that he would have in their removal.

In cancer of the large intestine the irritation caused by material which has escaped into small mucus pockets or diverticula exerts a chronic irritation which is one of the rather frequent determining factors in the causation of cancer of the colon. A high percentage of the patients subjected to operation for the removal of cancer in this region have been cured.

Surgical investigation, like Hunter's pathology, was based upon the macroscopic evidence of disease. The surgeon exposed the parts to sight, and, after making his examination, proceeded as appearances seemed to indicate. Unfortunately, correct information concerning the nature of the process could not always be obtained by such examination. The exact condition was revealed some days later by microscopic examination, but at a time too late to benefit the patient.

By the aid of the microscope and frozen section, as perfected by Mixter and Whitney in this hospital, the surgeon's vision has been extended into the minute structures of the processes of disease during the progress of the operation. This innovation in surgical pathology is of the greatest importance, since it enables the surgeon to be guided by the microscopic as well as the macroscopic aspects of the condition.

The sense of sight was also being brought to bear upon various organs by means of instrumentation as well as by surgical operation. The ophthalmoscope and laryngoscope permit exact investigation and supplant supposition with demonstrable facts. By the aid of the esophagoscope the esophagus is brought into view, and the terminal portion of the intestinal tract can be viewed through the proctoscope and sigmoidoscope.

The urinary bladder, which was supposed to be so often diseased, was found upon inspection through the cystoscope seldom to be the seat of primary lesions, although for years subjected to unavailing treatment for secondary conditions. Based upon clinical findings, tuberculosis was believed to involve both kidneys in the large majority of cases, and it was therefore believed to be a hopeless condition from its inception. This conclusion was apparently demonstrated by the fact that both kidneys were usually found to be involved at postmortem, an opinion later disproved by means of the cystoscope and the ureteral catheter, which in the majority of cases showed the disease to be unilateral until a late stage, and the second kidney involved by a terminal infection shortly before death. This knowledge converted an incurable into a curable disease.

In the process of building up living pathology, experimental investigation has been an important factor. It reconstructed physiology through vivisection. Pavlov, Starling, Cannon, and others demonstrated the nature of the digestive processes in the living, without which knowledge pathologic perversions could not be understood. The criticism which, in the beginning, pursued the scientist in this field of research is now passing away. More humane and highly scientific methods of investigation have gradually brought the fair-minded individual to view vivisection as a legitimate and, at present, the only sure means of obtaining certain important truths to aid in the preservation and prolongation of human life. As these methods continue to develop toward a more perfect science, so will adverse comment and opposition to its practice disappear.

Surgery within the cranial cavity and of the spinal canal has been greatly improved within recent years by surgical experimentation. The work of Horsley, Cushing, and others has lighted up the gloom which existed in this field, and many intracranial conditions formerly considered hopeless have been converted into surgical triumphs.

In the thoracic cavity advances have also been made through knowledge obtained by experimental surgery. Methods of preventing the collapse of the lung upon opening the cavity of the chest have been evolved by Sauerbruch and Meltzer by means of animal experimentation, which enables direct attack on the lungs, pleura, heart, and great vessels.

The work of Carrel, Crile, and Matas in experimental surgery of the blood-vessels reveals another field of scientific progress. Heretofore surgery has been associated with purely pathologic problems, but it is now attacking problems in physiology. I will but mention the transplantation of organs, which has been successfully accomplished in animals, as one of the possible means by which diseases now beyond the reach of human endeavor may be relieved.

At the close of the nineteenth century a discovery which may be classed with anesthesia and the germ origin of disease was brought out. Röntgen added another means of extending the use of the eye to the study of disease, and the *x*-ray has disclosed many of those inner secrets which have heretofore baffled alike the clinician and the surgeon. This agent has made possible the investigation of numerous conditions which previously could not have been made without operation.

We can readily understand the importance of the *x*-ray in the development of a living pathology. For the first time in the history of medicine diseases of the bones and joints could be inspected directly, and at an early and curable period, when a return to the normal was possible. By its aid fractures, dislocations, and similar traumatisms of the osseous framework could be restored without those deformities which so often occurred in the past.

The *x*-ray also added greatly to our knowledge of the hollow viscera, and often revealed processes which heretofore were discoverable only by the aid of the knife.

Diseases of the thoracic cavity were marvelously revealed. Surgery could not claim the triumphs in the thorax it had achieved in the abdomen, and until the *x*-ray enabled us to view the heart, lungs, and pleura, our actual knowledge of the living pathology as it might occur in this region was less than in the abdomen. Even in the cranial cavity, with its dense covering, the *x*-ray has been valuable in locating tumors and other diseased conditions.

One far-reaching result of these newer methods of investigation has been the development of medicine as a whole. Specialists of the past generation attempted to divide man into parts for examination and treatment. Today our subdivisions are more minute because of a wider knowledge, but no part stands alone as in days gone by. So vast is the extent of knowledge to be gained of disease that no one man can hope to accomplish more than a small share during his lifetime. The old-time family practitioner has passed away, and with him has passed individualism in medicine.

By what means can this great accumulation of the knowledge of disease be applied to aid individual patients? There is but one answer to the question—coöperation in medicine. Medicine must no longer be practised individually, but by groups of men, each one bringing the result of his work and studies to bear upon the case. In no other way can the patient receive the benefits to which he is entitled. How this coöperation can be satisfactorily brought about is our present problem. In foreign countries the State has been the controlling agent. Resources of medicine are brought to the aid of the sick by coöperative effort through the various clinics. Unfortunately, this privilege is accorded only to the charity patient and the poorer working classes. The so-called well-to-do are not eligible to this form of treatment, and are forced to the private clinics, many of which have not the necessary facilities for diagnosis and treatment.

In our own country the initiation of a progressive policy appears to be coming from the medical profession. The staff of our large hospitals coöperate in the treatment of charity patients quite as is the custom abroad, but there is a strong tendency toward coöperative service for the private patient as well, and groups of men are joining their forces for this most beneficial purpose.

The nineteenth century worked for the individual. One by one each disease was investigated and the results applied to the relief of the individual patient. The twentieth century starts out with a broader conception of the function of medicine. It is working for the masses in the prevention of disease. Care of the public health has become the most important duty of the State.

THE MICROSCOPIC EXAMINATION OF FRESH TISSUES FOR THE DIAGNOSIS OF EARLY CANCER*

LOUIS BLANCHARD WILSON

Cancer of important organs has for years been attacked with all the daring, intelligence, and skill at the command of our best surgeons. Radical operations have become more and more radical, until it would seem that the surgeon has for some time reached the extent to which he may go in the excision of tissues supposedly invaded by malignant growth from a known site, and yet constantly is the surgeon brought face to face with the fact that, once a cancer has invaded the lymphatics at any considerable distance from the initial site, it is almost a hopeless task to attempt completely to eradicate it. More and more are we coming to recognize that widely disseminated carcinoma is incurable by the knife, and, for that matter, as yet by any other process.

Along with this knowledge has come more and more evidence that when a carcinoma is, clinically, positively diagnosable, it is all too frequently widely disseminated, whether it be by the lymphatics alone, as in involvement of the axillary glands in carcinoma of the breast, or additionally, through the blood-vascular system, as in involvement of the liver secondary to carcinoma of the sigmoid and rectum. The danger of the distant distribution of carcinoma cells, even in cases in which the primary neoplasm is relatively small, is one ever to be reckoned with. In the young individual with wide-open lymphatics this is especially true. The woman under thirty-five years of age with carcinoma of the breast who lives more than two years after its discovery, however early and however radical the extirpation, is almost unknown.

---

* Abstract of an address before the St. Louis County Medical Society, Duluth, Minn., April 11, 1912. Reprinted from the "St. Paul Med. Jour.," June, 1913.

In all our study of the etiologic relationships of cancer, no line of investigation during the past decad has yielded more illustrations or more convincing proof than that carcinoma, whatever may be its hypothetic specific cause, most frequently develops at the site of previously existing chronic irritative lesions. While the term "precancerous" condition is open to the charge of being scientifically inaccurate, since such conditions frequently exist without the subsequent onset of any malignant process, yet the term, conveying as it does a full half-truth, and at the same time a sharp warning, is worthy of retention. These "precancerous" conditions, so far as carcinoma is concerned, seem to have one common basic element, namely, chronic irritation of epithelium, with secondary formation of scar tissue, and the segregation, by the scar tissue, of masses of epithelium.

In the skin, chronic ulcers of simple, syphilitic, or tuberculous origin, nodular keratoses, warts, etc., are the principal lesions on which malignant processes develop. The importance of these seemingly benign lesions in relation to cancer of the skin cannot be too strongly urged. Indeed, it is doubtful if cancer of the skin ever begins directly in normal tissue. There is always to be found the gross or microscopic evidence, or the undoubted history, of a "precancerous" condition.

Similarly, careful search has revealed that in cancer of the alimentary canal, in all regions from the lips to the anus, a very high percentage of cases show undoubted evidence of a preëxisting chronic irritative process at the site of the malignant lesion. On the lips[1] these may be ulcers, or areas of thickened epithelium from the smoker's pipe. On the tongue[1] and inner cheek walls ulcers from jagged teeth, leukoplakia, and syphilitic lesions are the most frequent bases. In the stomach and duodenum[2] we have shown chronic ulcers most frequently to precede carcinoma, while in the large bowel, particularly the sigmoid and rectum, the chronic irritation around diverticula[3] is the most frequent site of carcinomas.

Of the urinogenital organs, the kidney[4] frequently harbors stones prior to the development of flat-celled carcinoma of the renal pelvis, and the bladder is usually the site of much chronic irritation of its mucosa prior to the development of carcinoma within it. The careful study of the relationships of prostatic hypertrophy[5] and prostatic carcinoma will convince any observer of the constant implantation of the latter upon the former. The direct evidence of the segregation of epithelium in the uterus and vagina precedent to the development of malignant neoplasms is exceedingly difficult to obtain. However, well-authenticated instances of this are now accumulating, and, when one considers the frequent irritative and ulcerative processes present in the uterine and vaginal mucosa, with the necessarily attendant formation of scar tissue which can so readily isolate deep-lying epithelium, especially in the uterine walls, one is inclined to grant the probability of the constant presence of "precancerous" lesions of these organs in females of the cancer-bearing period. The frequency with which carcinoma of the breast develops in the walls of long-standing benign adenomas, or in epithelium isolated by inflammation, or as a result of abnormal senile atrophy,[6] has been frequently demonstrated in our clinic as well as elsewhere.

Starting now with the first premise previously laid down, that it is only in early undisseminated cancer in which the surgeon may hope for cures, and adding thereto a second, which is obvious from what has just been stated, namely, that "precancerous" conditions should receive the surgeon's attention, we readily perceive how important it is, both for the good of the patient and for the sake of scientific accuracy in judging our results, that we have as accurate a diagnosis as possible of the presence or absence of cancer tissue within these questionable lesions. This brings us face to face at once with the necessity for the microscopic examination of the tissue, since, when the neoplasm has reached the stage in which it may be accurately diagnosed grossly, it is not only no longer questionable, but it has also too frequently destroyed the evidence of the "precancerous" lesion and also passed the hope of permanent cure. There is no doubt that, so far as the accurate determination of the presence of a few carcinoma cells is concerned, it may best be done by the examination of thin serial sections of fixed tissue. Unfortunately, however, such an examination as this is of value only for statistical purposes, and wholly useless to the patient from whom the tissue is taken. The delay necessary for the fixing, embedding, cutting, staining, and examining of tissue by the older ordinary methods is so great that the patient's only opportunity of cure has been lost before a complete operation can be advised and consummated. The surgeon must know, while the patient is yet on the table, whether or not the questionable lesion is inflammatory or neoplastic, and he must then and there limit or extend his surgical procedure in accordance with this knowledge.

The study of unstained and variously stained fresh tissues in frozen sections is not new. However, I believe we may claim to have developed the technic at the Mayo Clinic a little more accurately, and to have carried it out more persistently than has been done elsewhere. Beginning seven years[7] ago, we have made a routine immediate examination of all questionable tissues removed at operation by cutting frozen sections, staining them momentarily with polychrome methylene-blue, washing in salt solution, and mounting in Bruns' glucose medium. This has meant the examination of many sections from a large number of cases every day. By such experience one becomes skilled not only in the preparation of the tissues, but, what is much more important, in the interpretation of the microscopic pictures seen in the sections. For several years every specimen examined by the fresh method was subsequently examined also in fixed tissues for confirmation of the diagnosis given from the fresh specimen. Recently, however, the results of these double examinations have given us such confidence in the pictures presented by fresh tissues that it is only in doubtful cases, such, for example, as the differentiation between round-cell sarcoma and infectious granuloma, that the diagnoses are postponed until fixed tissues can be prepared. Epithelial cells themselves can be quite as accurately differentiated from connective-tissue and other cells when stained by the method indicated above as they can be when stained by hematoxylin and eosin after fixation. Since the diagnosis of carcinoma depends upon the identification of epithelial cells and the determination of their position within the tissue, it will be readily understood that any method which permits of these two steps permits of accurate diagnosis.

That the method has its limitations there can be no doubt. It is impossible, within the usual five minutes which the surgeon is willing to wait, for the pathologist to examine microscopically every portion of the tissue submitted. He has to develop to the highest point his knowledge of the gross appearance of carcinoma in order to determine the areas in the tissue submitted which will most probably yield microscopic evidence of carcinoma. He must remember that every malignant neoplasm begins as a few cells, and not as a large mass. It is thus readily conceivable that the pathologist may overlook minute masses of early carcinoma, even when the entire mass of questionable tissue is in his hands. Further, the surgeon may not always submit to the pathologist that portion of the tissue which contains the evidence of cancer. Yet with these two large opportunities for error always open, it is remarkable how very infrequently it has been necessary for us to revise our initial diagnoses by the subsequent examination of fixed tissues.

In our fight against that most destructive and most insidious disease of man, cancer, it seems to me that the present state of our knowledge indicates three procedures:

1. There should be widely disseminated, both among physicians and laymen, the knowledge that carcinoma usually arises in epithelium which has been isolated by chronic irritative and ulcerative conditions of the skin, of the alimentary canal, or of the urinogenital system. With this should go the knowledge that operation, before wide-spread glandular involvement occurs, offers the only hope of permanent cure, and hence there should be no delay in securing an accurate diagnosis in the presence of "precancerous" lesions.

2. An accurate microscopic diagnosis of the presence or absence of carcinoma should invariably be made while the first operation is

in progress. Every hospital in which operations on tumors are done should have a laboratory as well as an operating-room, and a trained pathologist as well as a trained surgeon. The absence of either will some time come to be recognized as criminal negligence.

3. In early carcinomas, which are the only hopeful cases, the surgeon must be guided as to the extent of his operation by the report of the pathologist's microscopic examination. Naked-eye appearances of seemingly innocent growths are often deceptive, and the surgeon's unwarranted confidence in his knowledge of gross pathology may be the cause of the unnecessary loss of lives which could be saved did he but know at the initial operation that he is dealing with a malignant neoplasm.

REFERENCES

The following papers contain data from the Mayo Clinic relative to statements made in the foregoing paper:

1. Wilson and Willis: "Pathological Relationship of Ulcer and Carcinoma of the Alimentary Canal," "Jour. Amer. Med. Assoc.," 1910, vol. lv, pp. 921–923.
2. Wilson and MacCarty: "Pathologic Relationship of Gastric Ulcer and Gastric Carcinoma," "Amer. Jour. Med. Sci.," 1909, vol. cxxxviii, pp. 846–852.
3. Wilson: "Diverticula of the Lower Bowel, Their Development and Relationship to Carcinoma," "Annals of Surg.," 1911, vol. liii, pp. 223–231.
4. Wilson: "The Embryo-genetic Relationships of Tumors of the Kidney, Suprarenal, and Testicle," "Annals of Surg.," 1913, vol. lvii.
5. Wilson and McGrath: "Surgical Pathology of the Prostate," "Surg., Gyn., and Obstet.," 1911, vol. xiii, pp. 647–681.
6. MacCarty: "Carcinoma of the Breast," "Trans. South. Surg. and Gyn. Assoc.," 1910, vol. xxiii, pp. 262–270.
7. Wilson: "A Method for the Rapid Preparation of Fresh Tissues for the Microscope," "Jour. Amer. Med. Assoc.," 1905, vol. xlv, p. 1737.

FATAL POSTOPERATIVE EMBOLISM*

LOUIS BLANCHARD WILSON

INTRODUCTION

The plugging of vessels by foreign bodies floating in the bloodstream was first brought to the attention of the medical world by Virchow, to whom, indeed, we owe practically the whole theory of embolism.

His studies, made principally from 1846 to 1856, were early confirmed by numerous clinical, experimental, and postmortem observations by others, chief among whom should be mentioned Cohnheim and Cohn. Of the latter's work, published in 1860, Welch remarks: "It is extraordinarily rich in anatomic, experimental, and clinical facts, and it is well for any one who believes that he has a new observation or opinion concerning embolism to consult it before venturing on publication—a precaution which has evidently been often neglected by writers on the subject." When with Virchow's and Cohn's work we place Cohnheim's "Studies on the Embolic Process," published in 1872, and Welch's classic review of "Thrombosis and Embolism,"† published in 1899, we have listed most of the significant literature on embolism.

It is, therefore, not with a hope of adding materially to any portion of the doctrine of embolism that I present the following data, but merely to place it on record that it may be used for statistical purposes in surgical prognosis, and as a basis for suggesting anew certain precautionary measures for the prevention of embolism.

---

*Presented before the Association of American Physicians, May 16, 1912. Reprinted from "Annals of Surgery," December, 1912, pp. 809–817.

†Welch: "Allbutt's System of Medicine," 1899, vol. vii, pp. 155–285.

ANALYSIS OF CASES

From the opening of St. Mary's Hospital, September 30, 1889, to September 13, 1899, a period of ten years, I find no fatal case of postoperative embolism recorded in the annals of the hospital, and no sudden death which could reasonably be ascribed to such a cause, though during these ten years over 6000 major operations were performed in the clinic.

From September 13, 1899, to December 31, 1911, 47 fatalities from postoperative embolism occurred. During this period of twelve and one-quarter years approximately 57,000 major operations were performed.

Autopsies were made on 41 of the fatal cases, and the clinical diagnoses were quite positive in the remaining 6 cases. Within the same period it is true that a great many non-fatal cases of embolism were noted clinically with more or less positiveness, but the histories in many of these are too indefinite to warrant their tabulation along with the fatal cases, and a review of them is reserved for a later communication.

The cases have been grouped by years in Table 1 as follows:

The total number of deaths occurring in the hospital for the period under consideration, from all causes, was 864, of which the fatalities from embolism are approximately 5 per cent. The mortality from embolism, based on the 63,573 operations, is 0.07 per cent., or one death in every 1352 operations. When the cases are grouped according to the anatomic regions on which the preceding operation was done, they are found to be as follows:

After 1372 operations on blood-vessels, 2 deaths, or 0.14 per cent.

After 3266 operations on the thyroid, 2 deaths, or 0.06 per cent.

After 2281 operations on the mouth, 1 death, or 0.05 per cent.

After 2391 operations on the stomach or duodenum, 3 deaths, or 0.12 per cent.

After 4597 operations on the gall-bladder, 9 deaths, or 0.19 per cent.

After 389 operations on the small intestine, 1 death, or 0.26 per cent.

After 9908 operations on the appendix, 4 deaths, or 0.04 per cent.

After 2530 operations on the colon and rectum, 5 deaths, or 0.2 per cent.

After 4501 operations on hernia, 5 deaths, or 0.11 per cent.

After 900 operations on the kidney, 1 death, or 0.11 per cent.

After 601 operations on the prostate, 4 deaths, or 0.66 per cent.

After 7993 operations on the uterus, tubes, and ovaries, 10 deaths, or 0.13 per cent.

Total, 40,449 operations, 47 deaths—average, 0.12 per cent.

No fatality from embolism occurred in any of the 1346 operations on the breast, though a large share of these were extensive Halsted amputations. Neither did any fatal embolism follow any of the 449 vaginal hysterectomies, though there was one case in every 342 abdominal hysterectomies, that is, 5 in 1712 cases.

The following are some of the salient facts shown in Table 2:

Twenty-six of our patients were males and 21 females. The youngest was twenty-five years of age, the oldest, seventy-two, and the remaining cases were quite evenly distributed throughout the intervening decads.

Forty-one of the patients—all except 4 of the hernia cases and 2 of the appendix cases—had been from two to thirty-five years subject to some form of severe chronic debilitating disease. Speaking broadly, all these were very sick patients when operated on, and, in the light of our present knowledge, the majority of them were probably the subjects of low-grade bacteremias.

Nineteen of the fatalities occurred within the first week after operation, 21 more within the second week, 4 in the third week, and 1 each on the twenty-sixth, the thirtieth, and the sixty-fourth days, respectively. These latter three patients had all left the hospital and were well along in convalescence. In general, in marked contrast to the serious preoperative conditions of these patients, it was noted that they were getting along remarkably well just prior to the occurrence of the fatal embolism. These patients, however, were not kept in bed either a materially greater or a materially less time than were other patients having the same type of operation.

In 36 of our cases the embolism was pulmonary, in 10 cerebral, and in 1 coronary. In 28 of the 41 cases examined at autopsy the location of the originating thrombus was found in the field of operation or femoral vein. In 4 cases the emboli were found to have originated, in all probability, in the heart, and in the remaining 9 cases the source was undetermined. Arteriosclerosis was found in 5 cases, chronic myocarditis in 11, chronic nephritis in 14, and chronic hepatitis in 18. In 5 of the cases thorough postmortem examination failed to show any considerable change in any tissue or organ except those incident to the healing of the wound and to the embolus itself.

Special Inferences from Above Cases

With these data before us, what inferences may be drawn therefrom? Why for the first ten years in the history of the hospital, during which time 6000 major operations were performed, were there no recognized deaths from embolism, while since that period one case in every 1213 so terminated? Neither the surgeons, the anesthetists, nor head nurses have been materially changed on the staff in that time, nor yet has their method of procedure been materially varied. The anesthetic has been ether since the foundation of the hospital, and always it has been given in the smallest amount possible to maintain anesthesia for only sufficient time to permit the rapid completion of the operation.

The only changes coincident with the increase are:

(*a*) In the nature of the operations. During the first ten years the number of operations on the stomach, gall-bladder, lower bowel and prostate, and of hysterectomies was small enough to come under the limit of probable fatality as measured by that of subsequent years. During the last twelve years a very high percentage of our operations has been on these organs, and it is subsequent to operations on these organs that most of our fatalities have occurred.

(*b*) The condition of the patient coming into the hospital and to the operating-table has materially changed since the first decad of the hospital's history. During the first ten years of the clinic a very large proportion of the surgical cases were drawn from the general family practice of the members of the hospital staff and were operated on before they were *in extremis*. During the last twelve years, however, the surgical material has consisted almost entirely of referred cases, with an ever-increasing percentage of those of the "last resort" type, and it is in this class of cases in which most of the emboli have occurred.

GENERAL CONSIDERATIONS

From a study of our cases and of the literature of other observers, I desire to call attention to the following brief general considerations concerning the subject of postoperative embolism:

1. Following operations, particularly on the blood-vessels, alimentary canal, and genito-urinary organs (both male and female), from 1 to 2 per cent. of all cases give more or less distinct evidence of emboli, above 70 per cent. of which are in the lungs. Our own data in this regard have not yet been accurately tabulated, but they do not seem to give as high percentages as that from other clinics.

2. As nearly as can be observed from the incomplete and necessarily inaccurate data at hand, about 10 per cent. of postoperative emboli which give clinical symptoms of diagnostic significance cause sudden death.

3. Where postmortems are made on cases of fatal postoperative embolism, the source of the emboli can be definitely determined as venous thrombosis in about 80 per cent. of the cases, as cardiac thrombosis in 10 per cent. of the cases, while 10 per cent. are scattering or undeterminable.

4. Though there must be more or less formation of venous thrombi at the site of every extensive surgical operation, yet it is probable that the long, loosely formed thrombi from medium-

sized veins are those chiefly concerned in embolism, and especially in fatal embolism.

5. When large, loose thrombi are once formed in a resting patient, any unusual exertion or change of position may cause a dislocation of large masses which become dangerous emboli.

6. The most important factors concerned in extensive post-operative thrombosis are as follows:

(*a*) *Injury of the Vascular Walls.*—Rupture of the intima by cutting, ligating, or clamping causes a rapid deposit of a fibrinous thrombus, which, however, is normally confined to an area close to the injury. Over this the endothelium quickly extends, covering the thrombus within a few days. It is probable that such small terminal thrombi, when endothelial covered, rarely, if ever, become dislocated and form emboli. There can be no question, however, but that the constantly present small thrombi in injured vessels form a nidus for the subsequent development of large, loose thrombi through the activity of other factors.

(*b*) *Slowing and Stagnation of the Blood-stream.*—After operations the rapidity and volume of the current in the veins are materially lessened for a considerable distance proximal to the first incoming venous radicles. Furthermore, the patient is usually kept quiet in a recumbent posture, thus reducing the force and rapidity of the heart's action and causing a general slowing of the blood-current throughout the entire vascular system, including the heart. When the blood-stream is slower or when a part of the vascular system is incompletely filled, a disarrangement of the blood-cells occurs, the white cells and platelets reaching the periphery of the stream and tending to attach themselves to the vascular walls. In addition to this, in the presence of obstacles or marked expansions, a whirling motion, as pointed out by von Recklinghausen, may be set up which further tends to the retardation of the blood-stream and to the deposition of its elements as thrombi.

(*c*) *Disintegration of the Corpuscles of the Blood from Toxic Substances.*—While such toxic substances are not definitely known, their presence is assumed from their apparent action in the severe secondary anemias and hepatic diseases. It has been suggested that this factor may account for the high percentage of postoperative emboli following operations on the gall-bladder. It has also been suggested that toxic substances reaching the circulation from extensive carcinomas may in this manner cause marked postoperative thrombosis. In this connection, however, we must not forget the rarity of postoperative emboli following extensive operations for mammary carcinomas.

(*d*) *Bacteremia.*—That bacteria and their toxins are the chief causes of extensive postoperative thrombosis, as well as thrombosis occurring in the course of infectious diseases, is now fairly well established. By no means all postoperative thrombi occur in the field of operation. Phlebitis and a resulting thrombus are all too frequent. The last decad has seen a very marked extension of our knowledge of the frequent infection of the blood-stream by bacteria. This is particularly so in chronic diseases with local infection. It is readily conceivable that bacteria within the blood-stream may have their virulence sufficiently reduced to prevent their setting up a local phlebitis until aided by operative traumatism of the intima, postoperative slowing of the blood-current, or, perhaps, even the effect on the leukocytes of a prolonged general anesthetic. Certain it is that many thrombi, which we were formerly wont to regard as "marantic," we have now come to know are of infective origin. In this connection the postoperative formation of cardiac thrombi (and therefrom pulmonary or cerebral emboli) on small areas of endocarditis is worthy of note. When a polypoid thrombus has been swept off from the wall of the heart, its remaining ragged base may be overlooked without the most careful search at autopsy. While emboli from such a source are by no means common, the possibility of their occurrence must not be forgotten.

7. The above-mentioned factors must determine whatever precautionary measures may be taken for the prevention of postoperative thrombosis and embolism. The following suggest themselves:

(*a*) *The reduction of vascular traumatism to a minimum* at

TABLE I, SHOWING TOTAL OPERATIONS, DEATHS, ETC., COMPARED WITH DEATHS

Region	1889 to 1893		1894		1895		1896		1897		1898		1899		1900		1901	
	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.
Vessels	11	..	...	..	2	..	5	..	22	..	22	..	43	..	57	..	61	..
Thorax and lungs	...	..	1	..	10	..	1	..	4	..	13	..	12	..	12	..	15	..
Thyroid	...	..	...	..	...	..	3	..	6	..	4	..	..	..	10	..	3	..
Mouth	38	..	5	..	18	..	25	..	34	..	38	..	20	..	30	..	24	..
Stomach and duodenum	9	..	2	..	1	..	4	..	11	..	12	..	16	..	26	..	59	..
Gall-bladder and liver	9	..	3	..	10	..	21	..	15	..	20	..	33	..	76	..	107	..
Small intestine	2	..	...	..	7	..	5	..	2	..	4	..	10	..	7	..	14	..
Appendix	9	..	10	..	11	..	24	..	43	..	50	..	96	..	183	..	303	1
Colon and rectum	21	..	46	..	34	..	41	..	62	..	69	..	82	..	90	..	101	..
Hernia	9	..	6	..	17	..	32	..	42	..	43	..	76	..	74	..	128	..
Kidney	4	..	5	..	11	..	9	..	12	..	16	..	22	..	22	..	26	..
Urinary bladder	5	..	2	..	4	..	1	..	5	..	5	..	9	..	9	..	4	..
Prostate	...	..	...	..	...	..	1	..	..	..	...	..	..	..	..	..	...	..
Breast	18	..	8	..	11	..	14	..	11	..	16	..	28	..	35	..	36	..
Uterus, tubes and ovaries	58	..	73	..	34	..	112	..	179	..	156	..	303	1	312	..	324	1
Totals	193	..	161	..	170	..	298	..	448	..	468	..	750	1	943	..	1205	2
Abdominal hysterectomy	5	..	4	..	13	..	12	..	15	..	31	..	39	..	34	..	31	1
Vaginal hysterectomy	...	..	...	..	...	..	14	..	8	..	9	..	12	..	17	..	13	..
Total abdominal operations	86	..	57	..	111	..	196	..	251	..	322	..	470	..	612	..	841	..
Total operations	1075	..	537	..	606	..	877	..	783	..	973	..	1644	..	1713	..	2124	..
Total deaths	15	..	1	..	5	..	6	..	10	..	12	..	13	..	21	..	27	..

FROM EMBOLISM, ST. MARY'S HOSPITAL. SEPT. 30, 1889, TO JAN. 1, 1912.

1902		1903		1904		1905		1906		1907		1908		1909		1910		1911		Totals	
Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.	Operations	Deaths from Embolism.
65	..	70	..	87	..	80	..	132	..	129	..	131	1	164	..	159	..	132	1	1372	2
16	..	14	..	26	..	21	..	28	..	31	..	36	..	35	..	50	..	52	..	377	..
18	..	34	..	31	..	36	..	135	..	247	1	439	..	551	1	702	..	1047	..	3266	2
36	..	33	..	95	..	147	..	138	..	234	..	252	..	318	..	428	..	358	1	2281	1
77	..	139	..	171	..	217	..	214	1	190	..	232	..	272	..	336	1	403	1	2391	3
149	..	217	1	308	2	329	..	385	..	444	1	528	2	589	2	654	1	700	..	4597	9
15	..	21	..	18	..	7	..	11	..	35	..	27	..	38	..	67	1	99	..	389	1
345	..	404	..	536	..	766	1	928	..	1151	..	1344	..	1334	..	1174	1	1197	1	9908	4
119	..	97	..	118	..	142	..	196	..	214	2	238	1	260	1	269	1	331	..	2530	5
150	..	172	..	206	1	294	..	420	1	556	1	636	2	524	..	594	..	522	..	4501	5
34	..	35	..	37	..	50	..	73	..	76	1	85	..	107	..	132	..	144	..	900	1
16	..	13	..	9	..	29	..	46	..	17	..	32	..	41	..	46	..	66	..	359	..
6	..	29	..	27	..	63	..	42	..	67	1	86	..	82	..	87	2	111	1	601	4
41	..	37	..	48	..	84	..	98	..	102	..	148	..	202	..	212	..	197	..	1346	..
287	..	360	..	454	1	514	..	720	..	755	2	663	..	806	..	967	2	916	3	7993	10
1374	..	1675	1	2171	4	2779	1	3566	2	4248	9	4877	6	5323	4	5877	9	6275	8	42811	47
51	..	58	..	79	1	97	..	130	..	175	..	173	..	240	..	257	2	268	1	1712	5
11	..	17	..	7	..	30	..	49	..	58	..	51	..	41	..	57	..	55	..	449	..
1074	..	1302	..	1788	..	2157	..	2750	..	3215	..	3647	..	5079	..	3990	..	4266	..	32174	..
2420	..	2640	..	3131	..	3836	..	4770	..	5553	..	6451	..	7177	..	8218	..	8745	..	63573	..
32	..	69	..	62	..	64	..	69	..	81	..	86	..	83	..	108	..	100	..	864	..

operation by the conservative occlusion of vessels, and the p vision of free drainage to prevent later extensive external press on vessels.

(*b*) *The encouragement of very early free movement on the pa of the patient* as soon as the nature of the operation and danger fro hemorrhage will permit, though it must be confessed that the reported results from various clinics of "getting the patient up early" are unconvincing as to the reduction of postoperative embolism. If it can be done early enough to *prevent* the formation of extensive thrombi, it would seem to be most desirable. If, on the other hand, the condition of the patient's blood, either from anemia or bacteremia, is such as to lead to the suspicion that extensive thrombi *may have already been formed* before it is possible to permit free movement on the part of the patient it would then seem the part of wisdom to keep the patient as quietly as possible in a recumbent position to prevent the dislocation of the already formed thrombi. All the surgeon's judgment may be needed, and even then be at fault, in thus steering between the Scylla and Charybdis of "getting the patient, up early" or "letting him have a long rest in bed." Either may be the worse thing or the better thing for the patient according to whether extensive thrombi have or have not formed. So far as I know, we have not yet sufficient data on which to base an accurate estimate of the time required in a given case for the formation of extensive postoperative thrombi. We do know, however, that such large, loose thrombi, once formed, are readily dislocated by a relatively slight exertion on the part of the patient.

(*c*) *The preoperative administration of drugs to increase the coagulability of the blood*, as, for example, calcium salts in hepatic disturbances, is of questionable value, so far as thrombosis and embolism are concerned. It has not yet been shown that the presence of calcium salts in the blood renders it less liable to form thromboses, though it may be true that their presence induces the formation of a more dense clot.

(*d*) *Measures looking toward the reduction of bacteremia* are certainly indicated as a preoperative precaution for the prevention

Office No.	Hospital No.	Name.	of h.	Days after operation.	Clinical cause of death.	Autopsy cause of death.	Total operations from region.	T de fr en li
A3876	24381	J. B.	908	2	Embolism	Cerebral embolism	....	
A 56079	......	F. T.	911	9	Embolism	Pulmonary embolism.	1372	
A776	23048	C. O. S.	907	4	Cerebral embolism	Cerebral embolism	....	
29528	......	R. B. W.	909	1	Pulmonary embolism.	Pulmonary embolism.	3266	
A 50247	39894	G. P.	911	6	Pulmonary embolism.	Embolism pulmonary artery.	2281	
A 18974	......	B. B.	1910	10	Pulmonary embolism.	Autopsy refused	....	
7968	......	M. G.	1906	1	Pulmonary embolism.	Embolism coronary artery.	....	
50487	......	M. R.	1911	12	Pulmonary embolus	Autopsy refused	2301	
2189	......	W. T. J	907	10	Pulmonary embolism.	Pulmonary embolism.	....	
A 9932	26036	G. G.	908	8	Pulmonary embolism.	Autopsy refused	....	
1545	......	W. H.	904	15	Pulmonary embolism.	Pulmonary embolism.	....	
1308 G.	......	B. S.	903	5	Pulmonary embolism.	Pulmonary embolism.	....	
A 20890	29499	H. T.	909	9	Pulmonary embolism.	Pulmonary embolism.	....	
A 7738	25259	H. T.	908	8	Pulmonary embolism.	Pulmonary embolism.	....	
A46474	38394	J. W.	1910	12	Embolism	Double pulmonary embolism.	....	
1127	......	C. E.	904	14	Embolism	Cerebral embolism	....	
A 3664	......	E. Z.	1907	8	Pulmonary embolism.	Autopsy refused	4597	
A 38550	35711	J. F.	910	..	Cerebral embolism	Cerebral embolism	389	
958J	......	W.	905	5	Peritonitis	Pulmonary embolism.	....	
A 41747	......	H.	910	2	Pulmonary embolism.	Pulmonary embolism.	....	
......	......	W.	901	8	Pulmonary embolism.	Pulmonary embolism.	....	
58714	......	G.	911	8	Pulmonary embolism.	Pulmonary embolism.	9908	
9663 G.	......	R.	907	17	Pulmonary embolism.	Pulmonary and cardiac embolism	....	
37405	35351	M.	910	30	Cerebral embolism	Cerebral embolism	....	
A 13039	30438	J.	909	1	Pulmonary embolism.	Pulmonary embolism.	....	
A 14596	27300	H.	1908	8	Cerebral embolism	Cerebral embolus	2530	
A 1396	29532	B.	909	19	Cerebral embolism	Cerebral and pulmonary embolism	....	
A 7855	25269	H.	908	9	?	Pulmonary embolism.	....	
A 10017	26150	S.	908	3	Pulmonary embolism.	Pulmonary embolism.	....	
1209 M	......	W.	904	7	Pulmonary embolism.	Pulmonary embolism.	....	
1379 J	......	L.	906	12	Pulmonary embolism.	No autopsy	....	
3099	......	J.	1907	6	Pulmonary embolism.	Pulmonary embolism.	4501	
A9828	26184		908	12	Pulmonary embolism.	Pulmonary embolism.	900	
A2803	23631		1907	1	Cerebral embolism	Shock or cerebral embolism	....	
A 38191	......		911	64	Pulmonary embolism.	Right pulmonary embolism	....	
A 35217	37529		1910	2	Pulmonary embolism.	Pulmonary embolism.	....	
A 37447	35407		910	10	Pulmonary embolism.	Pulmonary embolism.	601	
......	......		1901	3	Pulmonary embolism.	No autopsy	....	
......	......		899	20	Pulmonary embolism.	Pulmonary embolism.	....	
3690 G.	......		904	12	Pulmonary embolism.	Pulmonary embolism.	....	
37821	......		910	8	Pulmonary embolism.	Pulmonary embolism.	....	
A 35866	......		910	8	Pulmonary embolism.	Pulmonary embolism.	....	
A 1451	23192		907	6	Pulmonary embolism.	Pulmonary embolism.	....	
48404	39237		911	3	Cerebral embolism	Cerebral embolism	....	
9802 G.	......		907	6	Cerebral embolism	Cerebral embolism	....	
A 58996	42967		911	8	Pulmonary embolism.	Pulmonary embolism.	....	
A 53176	......		1911	20	Pulmonary embolism.	Right pulmonary embolism	7993	1

of thrombosis and embolism. Where possible, the preliminary destruction, as with a cautery, of local foci of infection should be considered. When the invading organism can be isolated and identified, a preliminary vaccination is suggested. Indeed, it is probable that in some instances such a preliminary vaccination might prove of material benefit to the patient in avoiding postoperative infections other than those of the vascular system.

COMPLICATIONS FOLLOWING SURGICAL OPERATIONS *

A REPORT OF THE COMPLICATIONS AND DEATHS IN A SERIES OF 5835 SURGICAL OPERATIONS PERFORMED IN THE MAYO CLINIC, ST. MARY'S HOSPITAL, IN THE YEAR 1912

E. H. BECKMAN

A perfect restoration to health with an uninterrupted convalescence is the end sought in every surgical case. When this convalescence is delayed by a complication, however slight, the result must be regarded as a failure to obtain that ideal for which all surgeons are working. For the past three years an accurate record of all complications occurring in the Mayo Clinic has been kept. This work was begun to determine the number of failures occurring in our work, and was undertaken primarily for the benefit of our own staff.

We publish these complications for the first time, realizing that failures are the stepping-stones on which real progress is founded. We hope to make a report of this kind each year, and trust that it will be of benefit to others engaged in surgical work, and that other clinics following this lead will make similar reports, instead of the brief reports of recoveries and deaths which are customary at the present time.

The 5835 cases here reported are the house patients (in-patients), and do not include the patients having minor operations (out-patients), of whom there were 1218. Therefore, these patients were the more serious type of cases, whose operations were

---

* Reprinted from "Annals of Surgery," May, 1913.

considered grave enough to require them to remain in the hospital for treatment.

Infections.—Infections following surgical operations may be regarded in two ways:

First, all patients may be considered as infected before any operation is performed, and when suppuration occurs, the surgical technic employed has failed to overcome the infection. In this theory, which is the correct one, the normal resistance of the individual tissues to pathogenic bacteria must be taken into consideration. It should be remembered that under normal conditions the tissues have a certain resistance against bacterial invasion, but when that resistance is lowered, for example, by prolonged sickness, a severe surgical operation, or long-continued absorption from a neoplasm, the normal bactericidal properties of the tissues are interfered with, so that the bacteria flourish and we say that the patient has an infection. An operative technic should be attempted which will interfere as little as possible with the normal functions of the tissues, so that their vitality, or, in other words, their resistance to pathogenic bacteria, is lowered as little as possible.

Second, many surgeons apparently regard the tissues of the body as being sterile, and when an infection occurs following a surgical operation, they at once assume that the offending organism has been introduced from some extraneous source. It must be remembered that pathogenic bacteria may be in the tissues or introduced from some outside source, or both, and it is only occasionally that the source of the infecting organism can be found.

For several years every infection occurring in St. Mary's Hospital has been reported to the pathologic department, and an endeavor made to trace the source of the infection, but seldom has any definite conclusion been reached. An infection has never been traced to the suture material used. In the following series of cases every wound which failed to heal by primary union was considered as an infection. Many of such discharged only a few drops of serum. A considerable number of such cases showed no growth in the cultures taken from the discharge from the wound.

It has not been possible to take cultures for bacteria in all cases operated on the past year, but we hope to give a complete bacteriologic report on all such cases in the future. Fortunately, there were no deaths the past year from wound infection.

The following table gives the number of infections in each class of operations, a total of 111, or a percentage of 0.019 per cent. for the 5835 patients.

	Number of Operations	Number of Infections
Appendectomy	977	32
Operations on tubes and ovaries	229	1*
Block dissection, neck	41	1
Cesarean section	6	1
Diverticulitis, sigmoid	1	1
Excision, ulcer of stomach	20	1*
Excision, angioma of neck	1	1
Gastro-enterostomy (anterior and posterior)	274	17
Halstead amputation, breast	101	4
Hernia (inguinal)	315	14*
Hernia (umbilical)	30	1
Hernia (ventral)	78	1
Hysterectomy (subtotal abdominal)	215	2
Hysterectomy (total abdominal)	38	3
Kocher operation, uterine prolapse	39	2
Ligation of superior thyroid arteries	363	7
Meckel's diverticulum	8	1*
Pyloroplasty	20	2
Resection of stomach	46	2
Spina bifida	3	1
Suture of spinal accessory and facial nerves	1	1
Sarcoma of thigh and inguinal glands	1	1
Shortening of round ligaments (retroversion) 41 ext., 119 int.	160	2
Thyroidectomy	875	8
Varicose veins	47	4
		111

It will be seen that there are a considerable number of infections in appendectomies. When we made small McBurney incisions, we rarely saw an infection. Now we make long straight incisions in a large number of cases and explore the entire abdomen in nearly every case, regardless of the incision. When a McBurney incision is made, the hand is also nearly always introduced to explore the abdomen. We have thought that the introduction of the hand through a small incision, which, of necessity, draws the skin-edges forcibly into the deeper layers of the wound, was a large factor in this increase of infection, and we are taking added precautions against such contamination. The value to the patient of having a thorough abdominal exploration whenever the abdomen is entered has more than offset the slight infections that have possibly originated from this procedure.

---

* One of these had the appendix removed also.

The escape of secretions from the stomach and intestines is another source of infection in operations on those parts of the alimentary canal. Nearly one-sixth of the total infections occurred following operations on these organs.

Pulmonary Complications.—Three cases showed symptoms of pulmonary embolism. There is a possibility of a mistaken diagnosis in these cases. In each instance there was sudden pain in the chest, accompanied by dyspnea, a rapid pulse, and pallor, followed in a few days by a cough, with which the patient expectorated blood-streaked material. These symptoms would indicate an infarct in the lung, with softening later in the area of the infarct. These emboli occurred in patients as follows: (1) A patient on whom a cholecystectomy had been done and who also had a shortening of the round ligaments. (2) A patient with varicose veins on whom an inguinal hernia had been repaired. (3) A patient whose common bile-duct had been drained.

The pulmonary complications have been classified into four groups:

GROUP I.—*Pleurisy.*—Patients who have a pain in the chest, with a slight rise in temperature or no fever and a slight cough. There is often no cough. Hot applications or strapping of the side usually relieve the patient. The symptoms, as a rule, last only a few days—rarely longer than one week. We believe that in patients operated on for conditions in the upper abdomen the pleurisy often is a result of the postoperative inflammatory reaction extending to the diaphragm and pleura.

GROUP II.—*Bronchitis.*—Under this heading are placed those cases which have an excessive secretion in the air-passages. Many of them have only a slight rise in temperature for a few days, and expectorate excessive amounts of mucous or mucopurulent material. Others have a temperature of 102° to 103° F., with increased respiration, but the symptoms quickly subside, and the temperature drops to normal in forty-eight to seventy-two hours. The physical examination discloses no areas of consolidation in the lungs. Some of these cases appear to be a congestion of the lungs, or more properly a congestion of the mucous membrane of the air-passages. An upright position, fresh air, and heat applied to keep the skin active are usually sufficient to bring speedy relief. Atropin is sometimes of marked benefit, and is about the only medication used.

Group III.—*Bronchopneumonia.*—In this group are the cases in which the inflammation has seemed to extend from the air-passages into the tissues of the lung. The physical examination shows areas of consolidation or congestion in the lungs. The convalescence in these patients is slower than of those in Group II. The temperature is irregular, and varies from normal to 102° F.

Group IV.—*Lobar Pneumonia.*—In this group are those patients who have a definite consolidation of the lung, with a temperature of 102° to 103° F. for a week or more. The temperature is more likely to subside by slow degrees than in the typical lobar pneumonia. We believe that septic emboli are the cause of most of these cases. They rarely begin earlier than the third or fourth day following operation. In addition to the above there were 6 deaths from pneumonia. We could not attribute any of these cases to the anesthetic.

The total number of patients having pulmonary complications was 89, or 0.015 per cent. If we included the out-patients, the pulmonary complications would be well under 0.01 per cent. It should be mentioned that ether is used almost exclusively in this clinic. The operations in which complications of the lungs occurred is shown in appended table (p. 743).

Thrombophlebitis.—The total number of cases having a phlebitis as a complication following operation was 16. Although we continually have a certain number of phlebitis cases following operation, we have not been able to determine any causative factor in this annoying complication. We have always taken a middle

PLEURISY

Appendectomy	4
Appendectomy and curetage	1
Choledochotomy, cholecystostomy	2
Nephrectomy	2
Resection of portion of transverse colon	1
Subtotal abdominal hysterectomy	1
Baldy Webster	1
Double hydrosalpinx, appendectomy	1
Removal of ovary and tube, Wiley Mann, curetage	1
Cholecystectomy and appendectomy	2
Permanent colostomy	1
Pelveolithotomy	1
Thyroidectomy	1
Ovarian cyst	1
Cholecystostomy	1
Posterior gastro-enterostomy	1
Total	22

BRONCHITIS

Cholecystostomy and appendectomy	2
Cholecystostomy	2
Posterior gastro-enterostomy	7
Nephrectomy	2
Appendectomy	5
Inguinal hernia	5
Ovarian cyst	2
Anterior gastro-enterostomy	1
Vaginal hysterectomy	1
Femoral hernia	2
Left tube and appendectomy	1
Thyroidectomy	4
Cholecystectomy	1
Double tube ovarian abscess	1
Transperitoneal excision of bladder	1
Ligation of superior thyroid artery	1
Excision and cautery of osteoma of femur	1
Total	39

BRONCHOPNEUMONIA

Inguinal hernia	1
Appendectomy and left inguinal hernia	1
Cholecystostomy and appendectomy	1
Appendectomy	1
Choledochotomy and cholecystostomy	1
Posterior gastro-enterostomy	1
Umbilical hernia	1
Total	7

LOBAR PNEUMONIA

Cholecystostomy, postoperative hernia	1
Cholecystostomy	2
Appendectomy	2
Wilms' operation	1
Cholecystostomy and appendectomy	2
Posterior gastro-enterostomy	2
Supravaginal hysterectomy	1
Entero-anastomosis	1
Total	12

course, so far as getting the patients out of bed early is concerned. Most laparotomy patients are kept in bed from eight to twelve days, except those having simple appendectomies, who are allowed to get up on the sixth or seventh day following operation. It will be seen from the following table that exactly three-fourths of these cases of phlebitis were in the left femoral or internal saphenous vein, and one-fourth in the right; none were double. This is about the usual proportion in our clinic. It has not been determined definitely that patients that have an infected wound or are infected at the time of the operation are more susceptible to phlebitis than so-called clean cases. We are often surprised to find a phlebitis develop in a patient who has otherwise had an ideal convalescence. In only one of the present series was there an infected wound. It will be noted that in one of these patients phlebitis occurred in the arm following an operation for perineal fistula. The other cases of phlebitis were in the femoral or internal saphenous vessels. Our usual treatment for this condition has been elevation of the leg, with hot applications. There were no cases of embolism following phlebitis the past year.

THROMBOPHLEBITIS

	Left	Right
Appendectomy	1	1
Appendectomy, curetage, perineorrhaphy	1	..
Cholecystostomy, internal Alexander, curetage	1	..
Drainage of pelvic abscess	1	..
Total abdominal hysterectomy	1	1
Gastrectomy	1	..
Cholecystostomy and appendectomy	1	..
Cholecystectomy	1	..
Kraske colostomy	1	..
Tube and ovary, appendectomy, Wiley Mann	1	..
Ovarian cyst	1	..
Mayo operation for prolapse	1	..
Ventral hernia		1
Cholecystostomy		1
Total	12	4

Surgical Rash.—Surgical rash occurred 5 times during the year. Certain authors appear to attribute this condition to the use of soapsuds enemata. It is rather surprising that this condition has not been observed more often, considering the fact that soapsuds enemata were used quite extensively in our clinic.* As we have observed the rash, it more often simulates a scarlet-fever eruption, although occasionally it resembles a well-marked case of urticaria.

Epididymitis and *orchitis* were noted four times in the following operations: Excision of myoma of the bladder, excision of carcinoma of the bladder, a suprapubic prostatectomy, and an inguinal hernia.

Acute dilatation of the stomach, which formerly was often seen, was encountered but once during the year, this being in a case of cholecystostomy and posterior gastro-enterostomy for duodenal ulcer. We believe that we have been able to avoid this serious complication by early and frequent washing of the stomach. Whenever a patient has vomiting or regurgitation of bitter fluid from the stomach, although there is no real vomiting, routine lavage is employed.

Scarlatina occurred once following a small skin-grafting operation. One patient on whom an appendectomy had been done had an arthritis which affected some of the joints, but subsided in a few days. A perineal abscess developed in a patient who had had an abdominal resection of the sigmoid. Another patient on whom a vaginal hysterectomy had been performed developed a general furunculosis. Three cases, one an amputation of the breast, one a block dissection of the neck, and the third a spermatocele, developed a mild cellulitis.

Three patients developed a tonsillitis following their operations —one was an abdominal hysterectomy, one was a ligation of the superior thyroid artery, and the third was a shortening of the round ligaments and perineorrhaphy.

*Soapsuds enemata are not now in routine use in the clinic.

TABLE SHOWING NUMBER OF OPERATIONS ON REGION OR ORGAN; THE OPERATIONS FROM WHICH THERE WERE FATALITIES, AND THE NUMBER OF DEATHS THEREFROM

	Total Number of Cases	Number of Operations	Number of Deaths
Operations on cranium	64	..	..
Craniotomy	..	9	1
Trephining for fracture	..	5	1
Operations on eye	187	..	..
Operations on face	569	..	..
Operations on neck	566	..	..
Sarcoma, glands, excision	..	3	1
Tuberculous glands excised	..	105	1
Operations on thyroid	1249	..	..
Thyroidectomy for carcinoma	..	2	1
Single ligation of thyroid vessels	..	363	5
Thyroid carcinoma, exploration	..	4	2
Thyroidectomy, goiter, including the thyrotoxic type	..	594	7
Thyroidectomy, exophthalmic	..	275	1
Operations on breast	285	..	..
Amputation for carcinoma (Halsted)	..	101	3
Operations on back	38	..	..
Operations on chest	66	..	..
Empyema, decortication of lung	..	4	1
Empyema, drain	..	8	1
Operations on rectum, such as hemorrhoids, abscesses, etc.	234	..	..
Operations on male genital organs	180	..	..
Minor gynecologic	599	..	..
Perineorrhaphy	..	178	1
Miscellaneous operations, such as tapping for ascites, abscesses, etc.	150	..	..
Operations on extremities	321	..	..
Femur, ununited, Lane splint	..	6	1
Halsted's metal band for occlusion of femoral artery	..	1	1
Operations on stomach	242	..	..
Gastro-enterostomy for chronic ulcer	..	40	2
Gastro-enterostomy, closure of	..	10	1
Gastro-enterostomy for carcinoma	..	31	2
Gastrostomy	..	8	1
Gastrectomy, partial, for carcinoma	..	46	5
Operations on first portion of duodenum	223	..	..
Gastro-enterostomy for chronic and subacute ulcer and its results	..	187	1
Acute perforating ulcer, sutured, and gastro-enterostomy	..	6	1
Ulcer excised and pyloroplasty	..	20	1
Operations on appendix	*977	..	..
Acute and suppurative appendicitis	..	347	2
Chronic appendicitis	..	446	1
Operations on small intestine	78	..	..
Resection of fistulas with obstruction	..	8	1
Intestinal obstruction, acute and chronic	..	13	3
Intussusception, ileum into colon, acute	..	1	1
Laparotomy for diffuse septic peritonitis	..	6	1
Jejunostomy	..	6	2
Traumatic rupture, small intestine sutured	..	1	1
Exploration, carcinoma, irremovable	..	1	1

Table Showing Number of Operations on Region or Organ; The Operations from which there were Fatalities, and the Number of Deaths Therefrom.—(*Continued.*)

	Total Number of Cases	Number of Operations	Number of Deaths
Operations on large intestine	108	..	..
Resection of large intestine, including rectosigmoid for carcinoma	..	41	6
Resection of sigmoid for colitis	..	1	1
Colostomy for carcinoma with obstruction	..	24	3
Enterostomy	..	2	1
Operations on rectum	38	..	..
Resection, posterior, for carcinoma	..	27	4
Harrison-Cripps operation for carcinoma	..	4	1
Operations on liver and gall-gladder	821	..	..
Cholecystectomy	..	255	5
Cholecystostomy for cholecystitis and stones	..	426	3
Cholecystduodenostomy	..	4	1
Choledochotomy, stones in common duct	..	96	5
Duodenocholedochotomy	..	1	1
Operations on pancreas	16	..	..
Operations for hernia	465	..	..
Inguinal hernia, including strangulated	..	315	3
Ventral hernia	..	78	1
Operations on ovaries and tubes	229	..	..
Laparotomy for intraligamentary cysts	..	1	1
Laparotomy for ovarian cysts, dermoid	..	13	1
Operations on uterus	533	..	..
Hysterectomy, abdominal, complete	..	38	1
Hysterectomy, supravaginal	..	215	3
Hysterectomy, vaginal	..	38	2
Hysterectomy, vaginal, and plastic operation for prolapse	..	39	1
Miscellaneous	85	..	..
Laparotomy for exploration, carcinoma	..	15	3
Operations on kidney and ureter	206	..	..
Nephrectomy for mesothelioma	..	9	1
Exploration of kidney, hydronephrosis and ureterolithotomy	..	1	1
Nephrectomy for pyonephrosis, with or without stone	..	38	1
Nephrectomy for tuberculosis	..	41	3
Operations on bladder and prostate	185	..	..
Cystotomy, suprapubic, for calculus and pyelitis	..	28	1
Cystotomy, suprapubic, for retention and cystitis	..	24	2
Carcinoma of bladder, suprapubic resection	..	2	1
Papilloma of bladder, malignant	..	6	1
Prostatectomy, suprapubic	..	79	4
Prostatectomy and cystostomy, suprapubic, for hypertrophied prostate, calculus, cystitis, and pyelitis	..	4	2
Total number of operations	8703	..	..
Number of deaths following operation	..	..	119
Cases not operated, but dying in hospital	..	..	5

Total number of patients operated upon	7053
Number of in-patients	5835
Number of out-patients	1218

DRAINAGE OF WOUNDS*

DONALD C. BALFOUR

Although the importance of the great principle involved in the drainage of wounds has been recognized for centuries, it was not until 1859 that the practice was systematically established by Chassaignac.[1] He made use of vulcanized rubber tubes for draining collections of purulent material, and introduced a method of dealing with such conditions which, in a modified form, is in use today. Since that time the use of drains has reached its maximum, and is now undoubtedly on the decrease. Wounds are drained mainly for the purpose of carrying off products the absorption of which would be harmful to the individual. With the rapid development of surgery the recognization of the importance of hemostasis, the careful handling of tissues, and a perfected aseptic technic, the indications for drainage are becoming less and less. This tendency is based on the fact that unless drainage be necessary it is more or less harmful, a point emphasized by Welch[2] in 1891.

The disadvantages in the use of drains are many, *e. g.:* (1) Adding the risk of mixed infection; (2) damage to the tissues locally; (3) injuries to nerves and vessels; (4) the possibility of a ventral hernia in abdominal incisions; (5) pressure necrosis of the intestine with fecal fistula; (6) delayed convalescence owing to retarded healing; and (7) the discomfort to the patient. These factors have played a large part in the gradual but certain diminution in the use of drainage for wounds.

Another important point in this connection is found in the management of acute conditions, particularly of the abdomen.

---

*Read before the Chic. N. W. R. R. Assoc., December 18, 1912. Reprinted from the "Railway Surgical Journal," May, 1913.

Surgeons generally are now recognizing the fact that a large number of patients with acute inflammatory processes can be carried safely through the condition by appropriate treatment into a subacute or chronic state. Heretofore this group of cases was handled as emergency cases, requiring extensive drainage, when by giving nature an opportunity to deal with the infection and operating on the case in the subacute or chronic stage drainage might be avoided entirely.

Even in acute conditions drainage is being less employed. For example, in an acute condition in the abdomen, such as a perforated appendix with diffuse peritonitis, many surgeons of large experience do not use drainage. When one observes how little material is actually drained in these cases, the advisability of using it becomes at least debatable.

Further evidence of the tendency of wounds to heal more satisfactorily without drainage is found in connection with nephrectomy for tuberculosis of the kidney.

W. J. Mayo[3] reports to have had much better results so far as the primary healing of wounds is concerned, and the consequent rapid recovery of the patient, since he has filled the cavities with normal salt solution and closed the incision without drainage. This is true also in the treatment of tuberculous conditions within the abdomen, since drainage here is especially liable to be followed by a fecal fistula.

In view of these facts it is probably safe to say that the use of drainage is decreasing and will continue to decrease until its proper indications become known.

Occasionally, factors occur in surgical work which make the employment of drains advisable. In certain abdominal conditions the introduction of a small drain may be indicated in order to establish a channel through which nature may throw off harmful products which may develop during convalescence. Again, in certain chronic inflammatory conditions, especially old pelvic disease, it is difficult and sometimes impossible to check the oozing from the raw surfaces. These patients have an easier and more rapid convalescence when a piece of rubber tissue is inserted to serve as an exit to the surface of any collection of blood, for should any infection be present, a hematoma would act as an ideal culture-medium.

When drainage is indicated, the choice of the drain rests with the individual preference of the surgeon. So far as drainage is concerned, glass is an ideal material, but its rigidity is a marked disadvantage and limits its use. Rubber is by far the most generally satisfactory material, and can be used in many forms—tubes, spiral, split tubes, bands, etc. Gauze, properly used, makes excellent drainage for the first twenty-four hours after operation, but after that time it acts as a pack, and it is a dangerous material to use in certain cases. After ureterolithotomy, for example, gauze drains have been known to cause a fistula, produced by the removal of the gauze, which tears away the plastic work of nature in closing the opening in the ureter. In other conditions, however, gauze can be employed to quarantine infected areas against contact with surrounding healthy tissues. In operations on the gall-bladder, where the surface of the liver has been left raw and oozing slightly, a strip of iodoform gauze lightly applied makes a satisfactory tampon. The use of capillary drains, such as catgut, silkworm-gut, silver wire, etc., is popular only with a limited number of surgeons. Combination drains, such as cigarets, dressed tubes, split tubes, and gauze, are often employed for a definite purpose. The dressed gall-bladder tube is ¼ inch in diameter, surrounded by loosely wrapped iodoform gauze and an outer covering of rubber tissue. This permits of a purse-string closing of the gall-bladder to the tube without constricting it, and the rubber tissue casing insures its easy removal after several days.

The length of time drainage should be used is, of course, dependable on the individual case, but in a general way one could say that, so long as a drain acts as a drain, it is useful. The replacing of drains after removal is rarely advisable and usually harmful. After the primary drain has been removed, we are in the habit of filling wounds with vaselin or castor oil and balsam of Peru, according to the original idea of Van Arsdale. This lubricant prevents the wound healing at the surface, where the tissues are healthy, before the more dependent portions of the wound at the site of the focus of infection are unobliterated, which would pocket off infectious material without easy access to the surface. This practice has superseded the old method of repacking wounds after the original drain was removed, and is obviously of great advantage in securing easy and satisfactory healing of the drain tract.

REFERENCES

1. Pilcher: "Treatment of Wounds," p. 175.
2. Welch: *Loc. cit.*
3. Mayo: "Surg., Gyn., and Obst.," November, 1912.

NOGUCHI AND OTHER REACTIONS*

A. H. SANFORD

The detection of the "syphilitic antibody" by means of complement deviation has become such a common procedure that in every clinical center it is now regarded as a necessary laboratory test. It is safe to say, however, that there are very few men, in this country at least, who are following exactly, through all its cumbersome steps, the method of Wassermann, Neisser, and Bruck. These men originated their test after applying the well-known finding of Bordet and others regarding hemolysis.

By following the same principles, many have attempted to simplify the method with various changes in the original technic. Noguchi has given us by far the most important modifications. The salient features of the method are briefly as follows:

The Hemolytic System.—All complement deviation tests are based on hemolysis or its inhibition under certain conditions. Instead of a 5 per cent. suspension of sheep corpuscles, as in the old test, this method employs a 1 per cent. suspension of human corpuscles. The objection is raised that this indicator is much more delicate and that positive findings are, therefore, too common. This may be true to a slight degree in inexperienced hands, but, on the other hand, Noguchi points out the fact that at times human blood-serum contains a natural hemolysin for sheep corpuscles, and, as a result, a positive serum might give a negative reaction.

Amboceptor.—The specific hemolytic agent is prepared in the ordinary way, with the exception that washed human red blood-corpuscles, instead of sheep cells, are injected in increasing doses.

---

*Read before the Ramsey County Medical Society, June 24, 1912. Reprinted from "The St. Paul Medical Journal," September, 1912, pp. 461–471.

Rabbits are used, and are injected about every four or five days. As the cells are destroyed there is produced a great excess of the immune body, so that when the animal is bled, it is found that the serum, even when greatly diluted, contains a large amount of hemolysin. Often it is found that a dilution of 1:2000 or more will hemolyze 1 c.c. of a 1 per cent. suspension of red blood-cells.

There have been many complaints that there seems to be difficulty in getting an anti-human hemolysin of as high a titer as can be obtained against sheep corpuscles. However, with care, both in the choice of the rabbits and in the injections, this difficulty is more apparent than real. I have had no great difficulty in getting very active hemolysin by taking plenty of time for its production. It is true, however, that rabbits differ greatly in their individual power to produce an excess of immune bodies.

According to the side-chain theory, hemolysins are antibodies of the third order. They may combine with red blood-corpuscles at once, but have no power to act unless another factor, the complement, is present. The latter is the real active element, and the immune body is a connecting link. On account of this it is called an amboceptor. Noguchi has shown the great convenience of preserving amboceptor by drying the rabbit serum on ash-free filter-paper. When the amboceptor is prepared carefully, this method is reliable as regards the quantity required for hemolysis.

Complement.—The active element, complement, is present in all blood-serum, but not to the same degree. It is destroyed in a few minutes by a temperature of 56° C. For hemolytic tests it is customary to use the complement found in guinea-pig serum. Noguchi makes use of this in a 40 per cent. dilution arbitrarily using 0.1 c.c. as 2 units. However, there is a surprising difference in the activity of sera obtained from different guinea-pigs, and it is now the custom of many men to use the same quantity of amboceptor at all times, and to titrate against it the dilution of complement at hand for the day's test.

Patient's Serum.—In the Noguchi test the quantities of the reagents are so small that the serum may be measured by a capillary pipet. In using inactivated sera 4 drops, or 0.08 c.c., are taken. It has been shown that the so-called "antibody" is not entirely thermostabile, and while there is much left after twenty or thirty minutes at 56° C., there is at least 4 times as much in unheated serum. So with an active serum one drop from a capillary pipet (0.02 c.c.) is used. The amount of complement in this quantity of human serum is practically negligible.

Whether using active or inactive serum, the amount of blood required is much less than with the original Wassermann. Noguchi proposed that the blood be taken in a Wright capsule. However, this is a bothersome method, and the quickest and surest procedure is to take it from a large vein with a syringe.

The following has been our routine in the collection of blood: The patients all come to the laboratory at one o'clock on Thursdays. They have been previously instructed to abstain from alcoholic drinks for twenty-four hours and to omit luncheon. Blood taken during digestion of a meal may be too rich in lipoids, and Craig[1] has shown that alcohol may have such an effect upon the complement deviating body that a strong positive may become temporarily negative.

The patient's arm at the bend of the elbow is cleaned with benzin. When dry, tincture of iodin is applied to the skin, covering the group of prominent veins—the median basilic and cephalic, and their collaterals. A tourniquet above the elbow constricts the arm. The blood is then drawn as in taking a blood-culture. About 2 c.c. is placed in small sterile test-tube stopped with a sterile cork. At the same time some of the blood from several of the patients is put into a flask containing 100 c.c. of 2 per cent. sodium citrate in 0.9 per cent. NaCl solution. In this way corpuscles are obtained for the test and for injecting into the rabbits. It requires several washings and sedimentations with a high-speed centrifuge to free the cells entirely from serum. The test is made on Friday and the serum drawn off from the clotted blood at that time.

Antigen.—In place of the watery extract of luetic liver, many men used an alcoholic extract. Noguchi has shown that probably the Treponema pallidum plays no part in these antigens. He extracts normal tissue with alcohol, evaporating the filtrate to dryness, and takes up the residue with ether. This ethereal solution of lipoids is evaporated to small bulk and acetone added. A precipitate is immediately formed. This acetone-insoluble fraction is taken up with methyl-alcohol 0.3 gm. to 10 c.c. Noguchi's requirements for a perfect antigen are that four times the amount used in the test shall not in itself bind complement nor produce hemolysis, and that one-fifth the amount combined with the usual quantity of positive serum shall deviate complement. For immediate use a 10 per cent. mixture is made of the stock solution with normal salt, and 0.1 c.c. used for each serum tested.

It is not within the province of this paper to present any theories regarding the nature of the so-called "syphilitic anti-body." Suffice it to say that it is not truly a specific substance developed in an attempt at immunity against the Treponema pallidum. There are several reasons for this statement: First, the original Wassermann was reported to be positive with diseases other than syphilis, and this with an antigen that was supposed to be filled with the specific organisms. The tendency toward the general adoption of the Noguchi method of preparing antigen is another argument against the complement-fixation substance being an antibody. The presence of a bacterial immune body is demonstrable by complement fixation methods, the antigen being an emulsion of the specific organisms. Noguchi and others have not been able to show any antigenic properties in his emulsions of treponemas.

In many laboratories sera are set up, using both an anti-sheep cell method and the anti-human hemolytic system (Noguchi). In our laboratory, as we have difficulty in procuring sheep corpuscles and always have human blood, we use the Noguchi test almost exclusively.

Dr. Mullin did over 400 tests by this method for the Mayo Clinic up to August, 1911. Since that time, up to June 15, 1912, there have been 741 tests performed in our own laboratory. A complete analysis of all of these is impossible, but they may be arranged quite accurately in the following groups:

Total number reported	741
Total number negative (68 per cent.)	507
Total number showing inhibition of hemolysis positive (weak positive and faint positive) (32 per cent.)	234

The negative test may be arranged as follows:

No history of lues (54.6 per cent.)	405
History doubtful (2.6 per cent.)	19
History of lues, no recent treatment (3.8 per cent.) (1 female)	28
History of lues, recent treatment (4 per cent.) (6 females)	30
Second test negative, first positive	13
Second test negative, first negative	8
Third test negative	4
Total (68 per cent.)	507

The 234 tests showing various degrees of inhibition of hemolysis fall into the following groups:

Positive—history of lues (7.5 per cent.)	56 males	
Positive—history of lues (1.6 per cent.)	12 females	
Positive—history of lues, recent treatment (1.5 per cent.)	11 (1 female)	
Total (10.6 per cent.)	79	
Positive—no history of lues (3.8 per cent.)	28 males	
Positive—no history of lues (4.2 per cent.)	31 females	
Total (8 per cent.)	59	
Weak or faint positive (6.3 per cent.)	47 males	13 with history 34 no history
Weak or faint positive (3 per cent.)	21 females	1 with history 20 no history
Total (9.3 per cent.)	68	
Second test positive, first positive (3 per cent.)	22	
Second test positive, first negative (1 per cent.)	5	
Third test positive, first positive		

It is impossible at this time to analyze all the cases completely, as in some instances the diagnosis is still in doubt. Nearly always, however, the results have been in accord with the clinical diagnosis, or have made the diagnosis clear, and have pointed the way to treatment.

The 19 negative cases with doubtful history and the 28 with history and no recent treatment may be either cured or latent cases. Likewise, the 30 negative cases with recent treatment may at a future date give a positive reaction. The tests that were negative the second or third time show the effect of treatment. The eight cases negative after a previous negative were attempts to clear up doubtful diagnoses.

The negative cases with no history require no comment, except to say that they were sent in for symptoms that might be part of a picture of luetic infection, such as nocturnal headaches, suspicious eye symptoms, perforated septa, otitis media interna, chronic ulcers, pains suggestive of tabetic crises, etc.

There were but three cases with primary lesions seen during this time, only one giving a positive test. There were but four cases with secondary rash. The majority of the cases, then, that were positive were those with tertiary lesions, latent or congenital lues, or parasyphilitic conditions. It is not to be understood that every case showing inhibition of hemolysis is assumed to be some form of syphilis. Any laboratory test must be carefully considered with the clinical evidence. The strong positive, total inhibition of hemolysis, even when no history is obtainable, is, as a rule, diagnostic of lues. The weak and faint positives merit very careful consideration. It is recommended by Noguchi and most serologists that the patient be given the benefit of the doubt, and such cases be considered negative unless there is a history of lues or recent antisyphilitic treatment.

Of the 68 cases reported weak or faint positive, 14 in all, 13 males and 1 female gave a history of luetic infection. The balance, 34 males and 20 females, furnish a small but interesting group of cases. Several of these should be considered negative without doubt, and space forbids a complete analysis of the group. Suffice it to say that in many instances the patient was markedly benefited by antisyphilitic treatment.

Case I (63167).—Female, single, aged thirty-three. Iritis at thirteen. No history of lues. Punched-out ulcers on legs since five years of age. January 26, 1912, positive (weak). Given salvarsan, mercury, and potassium iodid. Ulcers completely healed. We have since learned from the family doctor that the father's early life was questionable, and two other daughters have stigmas of congenital syphilis.

Case II (60395).—Female, aged forty-six, married. Six children (healthy). No miscarriages. No luetic history. Deep recurring undermined ulcers on thigh. October 26, 1911, positive. Given "606" and mercury. January 29, 1912, patient reports the ulcers all healed and that she is feeling fine.

There were in all 9 patients with ulcers of the leg giving either a positive weak or positive reaction, and 16 similar cases that were negative. However, in the light of our present knowledge as regards the nature of the complement-deviating body, it is conceivable that occasionally an extensive chronic ulcer, non-specific, may give us some inhibition of hemolysis. This result has also been reported as occurring occasionally in cases of malignant tumors. We have not made a careful study of this point, but in the course of our routine examinations we have seen 27 cases of probable or known carcinoma and one of sarcoma give a negative test. There have been 7 cases in all, one a sarcoma, that gave either a positive or weak positive. One of these patients gave a definite history of lues. Another had had a sore twenty years ago pronounced a soft chancre by a very excellent physician in Europe. One of the patients, a married woman with carcinoma of the rectum, gave a weak positive on two different occasions and no history of lues. The husband's history was doubtful, however. The only case with a strong positive in the group was rather remarkable. This patient denied having had lues, but admitted having had gonorrhea three times. His serum was tested several times and totally inhibited hemolysis a month after its withdrawal, both when active and inactivated. The other three cases, including the case of sarcoma of the testicle, gave only faint positives and might be classed as negative. I will merely mention a few more of the interesting cases.

CASE III (60335).—Male, aged forty-four, traveling man, married, had initial lesion; treponemas found in great numbers. Serum test negative. Chancre healed quickly with "606." Three months later, with no history of any manifestations of the disease, patient's wife gave a strong positive. She was given salvarsan, and the next day a very characteristic secondary rash appeared. This cleared up quickly.

CASE IV (63812).—Male, single, aged sixteen. Came with "cold-sore" which he had had for three months. Lip swollen, crusted over, and foul-smelling discharge present. Submental, submaxillary, and cervical glands enlarged. There were no signs of secondaries. February 10, 1912, serum gave total inhibition (strong positive) and treponemas found in the chancre. He was given 3 injections of "606," mercury, and potassium iodid. March 1, 1912, patient discharged, practically free from any evidence of the disease.

Case V (65248).—Male, single, aged thirty-five, machinist. Lues ten years ago. Extensive ulceration of the larynx (pronounced tuberculosis). No tubercle bacilli found in sputum on four examinations. March 15, 1912, positive. Seven injections of salvarsan. As a result, the ulcers healed completely.

There were 9 cases diagnosed as tabes with negative reaction, and 15 cases of tabes, or other diseases of the nervous system, that were positive.

Case VI (63873).—Male, aged fifty, married. Denied having had lues. Had broken-down gummas about the left elbow. Argyll-Robinson pupils and slight Romberg. Knee-jerks were absent. Shooting pains down the legs for eighteen years. The cystoscope showed trabeculæ. Diagnosis: Tabes. February 10, 1912, total inhibition. Strong positive. Given "606." Gummata disappeared almost at once. Shooting pains still present.

Five times the test was positive in cases in which a previous test had been negative.

Case VII (63860).—Male. Diagnosis: Charcot joint. February 10, 1912, negative. Given salvarsan, mercury, and potassium iodid. April 5, 1912, positive.

Another case with specific ulceration of the larynx gave only a faint positive. Specific treatment improved the patient's condition, but the test became strongly positive. At a more recent examination there was still a faint positive, with both the subjective and the objective symptoms practically gone.

Another case, negative February 3, 1912, but with a history of lues and of recent treatment, was given salvarsan. The test was weak positive April 5, 1912, and negative June 7, 1912.

I have been asked to discuss other reactions. Fraser B. Gurd[2] has devised a modification that is ingenious, but not likely to come into general use. He employs the Noguchi antigen, but makes use of the small amount of natural amboceptor for guinea-pig corpuscles found in human serum. This is diluted to various degrees, and five tubes are necessary for the test for each patient. The complement and corpuscles are furnished by the same guinea-pig. The reaction is very delicate, and it is claimed by the originator to be somewhat quantitative, and therefore useful in watching the effect of treatment.

Emery's modification has some advantages claimed for it. He uses the small amount of complement present in human blood-serum. This necessitates doing the test within twenty or forty hours after withdrawal of the blood, as the complement soon disappears. Very small quantities of sera and reagents are used. A Wright pipet is employed for making the dilutions and setting up the test. Noguchi antigen is used by Dr. Stitt, of the Navy Medical School, and the test prepared with dilutions of the stock solution 1:20, 1:40, 1:80, etc. One volume of active serum is added to each tube, and incubation carried on for thirty minutes. At the same time one volume of washed human red blood-corpuscles is added to four volumes of amboceptor solution and incubated. Dr. Stitt uses the Noguchi method of drying amboceptor on filter-paper. One volume of the sensitized red cells is added to all tubes at the end of thirty minutes, and incubation again carried on until hemolysis occurs with the negative sera. This comes on very rapidly, and the whole test may be done in forty-five minutes. A tube without antigen is set up for control of the hemolytic system. It is thought, by those using the test, by graduating the amount of antigen that they obtain a quantitative determination of the amount of antibody present. It is a question, however, if the degree of fixation is not dependent chiefly on the amount of antibody present and not so much on the amount of antigen. This method has the advantage, however, of doing away with the guinea-pig and makes the test more serviceable for those distant from a fully equipped laboratory.

Richard Weil,[4] making use of the findings of Flexner and Noguchi, has devised a cobra-venom test for the diagnosis of syphilis. He found that the corpuscles of luetic patients are more resistant to hemolysis by snake venom than those of normal individuals. The patient's blood is placed in 2 per cent. sodium citrate, and washed very thoroughly four times. Weil insists that no other method of separating corpuscles from plasma than the use of sodium citrate suffices. One c.c. of a 4 per cent. suspension is placed in each of four tubes for the test. The cobra-venom is diluted 1:10,000, 1:20,000, 1:30,000, and 1:40,000, and 1 c.c. of a dilution placed in a tube containing corpuscles. Incubation at 40° C. for one hour usually is all that is sufficient to make a diagnosis. A strong positive is shown by complete inhibition of hemolysis at a dilution of 1:10,000. No hemolysis at 1:20,000 indicates a positive luetic serum. Hemolysis to any degree in the tube diluted 1:30,000 is a negative, and a strong negative is present if there be the slightest trace of hemolysis in the last tube—dilution 1:40,000. Weil and those who have used the test claim that it is much more active in latent syphilis than any hemolytic test. It also gives a positive longer after treatment than the Wassermann or Noguchi.

Cobra-venom is very expensive, as the supply on the market is limited. It is an active poison, of course, and must be used cautiously. The test is, however, exceedingly simple, and probably merits further trial.

Noguchi has given us two other tests that are worthy of consideration—luetin and the butyric-acid test. Luetin is made by grinding up a pure culture of Treponema pallidum in NaCl solution and sterilizing by heat. The emulsion is then injected intradermatically in a manner similar to a tuberculin skin-test. The reaction in case of lues is marked and quite persistent. Cases of latent lues are readily diagnosed by this method. It may be said that there are some things to be perfected about the test, especially a method of standardization of the activity of the emulsion.

The butyric acid test is applied best to spinal fluid. Five parts of 10 per cent. butyric acid in NaCl solution are added to 2 parts of the fluid and boiled. One part of normal sodium hydroxid is then added, and the mixture boiled again. A precipitate on cooling indicates an increase in the proteid content. This may be due to syphilis, a parasyphilitic condition, or an inflammation of the meninges. A consideration of the clinical symptoms, further examination of the fluid for organisms, and a count of the cell content may all be necessary for a diagnosis.

So-called "cytodiagnosis" is of some aid to a recognition of syphilis of the nervous system. A predominance of lymphocytes in a clear fluid indicates either cerebrospinal syphilis, tabes, or tuberculous meningitis. The clinical symptoms or the finding of tubercle bacilli should aid in establishing the diagnosis of the last-named disease. An increase in polynuclears points toward an acute meningitis, though in mixed infection there may be pus in a tuberculous condition.

The last decad has given us many scientific methods for detecting the presence of one of the most baffling of diseases. It may be said of all tests, however, that they should be weighed very carefully with the clinical evidence. Often therapeutic tests are still necessary to clear up doubtful diagnoses. Certainly the clinician and laboratory worker should know each other's work. The laboratory worker should know the clinical indication suggesting the examination, and the patient's physician should know the meaning of every phase of the report. By working hand in hand, the two should be able to go far toward arriving at the correct diagnosis, and carrying out the best treatment for the patient—the ultimate duty of medical science.

REFERENCES

1. Craig: "The Effect of the Ingestion of Alcohol on the Result of the Complement Fixation Test in Syphilis," "Jour. Amer. Med. Assoc.," August 5, 1911, pp. 474–476.
2. Gurd: "The Use of Active Human Serum in the Serum Diagnosis of Syphilis," "Jour. Infect. Dis.," June 15, 1911.
3. Emery: "Simplified Form of the Wassermann Reaction," "Lancet," September 3, 1910.
4. Weil: "On the Resistance of Human Erythrocytes to Cobra-Venom," "Jour. Infect. Dis.," November 25, 1909.

MALARIA IN NORTHERN STATES*

A. H. SANFORD

When the Northwestern States were unbroken prairies, and when the Mississippi River was the great means of travel into this region, malaria was not unknown clinically to the older physicians of Wisconsin and Minnesota. With the advance of civilization and the tilling of the soil the disease disappeared.

Our text-book and school instruction regarding regions in which *Anopheles* mosquitos breed have led us to believe that they are not to be considered north of central Illinois. Since the mosquito is not a migratory insect,—traveling only a few miles from its native swamp,—there is little danger of the spread of malaria northward.

Osler says: "In the Northwestern States malaria is almost unknown. . . . In the region of the Great Lakes malaria prevails only in the Lake Erie and Lake St. Clair regions."

Concerning the distribution in the United States, Nothnagel says: "Those lying more centrally and toward the Northwest, Ohio, Indiana, Illinois, Missouri, Iowa, Minnesota, Wisconsin and Michigan are less affected. . . . almost not at all on Lake Superior and Michigan. In Canada, except the northern shore of Lake Ontario (Kingston), the disease can scarcely be called endemic. It is found in Wyoming, Utah, and Colorado."

From the foregoing, it would appear that Minnesota and Wisconsin were possibilities as to the location of infection with plasmodia. However, a careful search of the literature has not revealed any reports of cases within the last eight or nine years, though the rarity of the infection in these regions surely calls for a recognition of the condition if it exists.

*Reprinted from "St. Paul Med. Jour.," February, 1913.

This report is prompted by the fact that we have had two cases in the Mayo Clinic recently—one from Wisconsin and one that had never been out of Minnesota.

Case 1 (A74448).—Male, aged two years. Residence and birthplace, Oronoco, Olmsted County, Minn. Consultation October 4, 1912. Referred by Dr. Granger and seen by Drs. Giffin and Archibald. Family history: An aunt (maternal) had pulmonary tuberculosis; there are four other children in the family, all of them well. Personal history: Patient had whooping-cough during the past spring and summer. For three weeks had been peevish and restless; had night-sweats and was feverish during the day. One week ago (September 27, 1912) the patient began to have spells which came on every day at 11 A. M. During these attacks he turns blue, has chills, and seems to be in pain. The attacks last one hour, and during the rest of the day he sweats and has fever. He seems to rest well at night. Vomited at first attack, but not since. There is no diarrhea and no blood in feces. He has a slight cough; appetite is good. Micturition normal. Physical examination: He is well nourished, but very pale: spleen and liver enlarged; examination of blood shows many active plasmodia in the fresh specimen; spreads stained with Wright's stain, and made about an hour before the chill, show many cells with the typical *Plasmodium vivax* inclusions; the appearance of segmentation simultaneously with single schizonts confirms the clinical history of double infection with the tertian type of parasites.

Case 2 (A74401).—Female, aged thirty-five years. Residence, Madison, Wis. Born in Michigan; lived in North Dakota a number of years, and went from there to Madison three years ago; has never been south of Madison. Consultation October 3, 1912. Physicians, Drs. Graham and Stacy. Family history: Mother had diabetes: Personal history: Has had four children, youngest nine years old; no previous diseases. Last week of July, 1912, was taken with a sudden pain in the back just below the waistline. There was not a great deal of pain in front. She had a gnawing feeling in the stomach after two weeks, but attributed it to medicine and hunger. Marked jaundice accompanied or preceded the attacks. She had chills and fever every other day for two weeks, but after that was free from pain. Quite well until three weeks ago (September 12, 1912), when a similar but lighter at-lymphocytes, 10 per cent.; polymorphonuclears, 55 per cent.; transitionals, 4.7 per cent.; eosinophiles, 3 per cent.; basophiles, 1.7 per cent.; many plasmodia in fresh preparation. Wright-stained slides show forms of *Plasmodium vivax*. Diagnosis: Malaria, tertian type.

Dr. L. F. Jermain, of Milwaukee, has reported two cases of malaria to the Milwaukee Medical Society. In a personal communication, Dr. Jermain says: "They were both contracted in the State of Wisconsin. Neither patient had ever been outside of the State. They were both observed during the summer of 1911. One was a saloonkeeper, aged thirty-five, who had never had malaria. He went on a fishing trip to Lake Keesus, in Waukesha county, remained there for two weeks, during which time he camped in a tent and was considerably annoyed by mosquitos. Upon his return home to Milwaukee he developed chills, high fever, and sweats, at first every forty-eight hours, later every twenty-four hours. He was treated for two weeks for typhoid fever. When I saw him he had daily paroxysms and was extremely ill, being delirious and somewhat jaundiced. Blood examination revealed tertian parasites. Prompt recovery followed the use of quinin—in fact, only one chill occurred after its administration. The second case occurred in a young man of twenty-two years who had never had malaria. He took a canoe trip down the Wisconsin River, from Grand Rapids to Portage, sleeping in a tent on the river bank at night. He developed simple tertian infection. The organisms were in abundance in the blood. This man did not take his quinin as regularly as he should, and a month later suffered a relapse. These are the only two cases of malaria that I have positive proof of as having been contracted in this State. Dr. Ogden tells me that he has found the anopheles in this State on numerous occasions, so that if we have the mosquitos, we are certain to have the disease."

In 1903 Dr. H. P. Johnson, then Professor of Bacteriology in St. Louis University, noted the presence of numerous *Anopheles* mosquitos in the vicinity of Ely, Minn.

It seems, then, that among diseases common in the South, but occurring sporadically in the North, we must place malaria. It would be well for physicians and sanitarians to be on the lookout for the breeding-places of the *Anopheles*, and not to lose sight of the possibility of a spread of malaria from those visiting the North from regions where the disease is prevalent.*

---

*Since writing the above my attention has been called to an article by Kennett Taylor, M.A., in the "St. Paul Medical Journal," July, 1910. Mosquitos of the Anopheles type were found in great numbers at that time in the vicinity of the Twin Cities.

NOTE ON A PEPTID-SPLITTING AGENT IN HUMAN BLOOD-SERUM*

FRANK SMITHIES

A Preliminary Report

The researches of Vaughan, Cumming and Wright,[1] and Nicolle and Abt[2] seem to indicate that proteins introduced into the peripheral circulation or serous sacs undergo what Vaughan terms "parenteral digestion." These workers consider parenteral cleavage of proteins a very important factor in the body's defensive mechanism.

Apart from the laboratory or clinical evidences that the blood and body cells split foreign proteid in a manner corresponding to its hydrolysis *in vitro*, we have not noted previous evidence that such cleavage is actually carried on in the circulation.

Recently, while studying the biochemic properties of blood-serum (particularly the sera from patients affected with some form of gastro-intestinal neoplasm), we had opportunity of investigating its action on the dipeptid, glycyltryptophan (Fischer[3]). This dipeptid is indol-alpha-aminopropionic acid (tryptophan) combined with glycocoll. It has been shown by Neubauer and Fischer[4] and Abderhalden[5] that glycyltryptophan is readily hydrolyzed by ferments and that the cleavage product, tryptophan, can be conveniently recognized in acid solution by admixture of bromin vapor.

We have found that when aseptically obtained, fresh blood-serum is combined with a solution of glycyltryptophan (Fischer) and incubated under toluol at 37° C. for twenty-four hours, on acidulation with 3 per cent. acetic acid, typical rose-pink to violet color changes occur on the admixture of bromin vapor. These color changes persist for varying lengths of time. Control serums heated to 80° C. previous to incubation do not give such glycyltryptophan reaction. Neither is such reaction obtained if serums are incubated alone, are mixed with absolute alcohol, 1 per cent. mercuric chlorid solution, 2 per cent. phenol (carbolic acid) solution, 0.25 per cent. alphozone solution, or antiformin.

---

*Reprinted from the "Jour. Amer. Med. Assoc.," August 17, 1912, vol. lix, p. 539.

Not all blood-serums split glycyltryptophan solutions with equal rapidity or completeness. There are some serums which have almost lost their power of splitting this dipeptid. These are frequently from patients not well. Varying dilutions of serum with normal salt solution or distilled water exhibit certain variations which seem to permit of a quantitative interpretation.

The agent in blood-serum causing the cleavage of glycyltryptophan appears to have the qualities of an enzyme.

REFERENCES

1. Vaughan, Cumming, and Wright: "Zeitschr. f. Immunitätsf. u. exper. Therap.," May 13, 1911, p. 458.
2. Nicolle and Abt.: "Ann. de l'Inst. Pasteur," February, 1908.
3. Fischer, E.: "Ber. d. deutsch. chem. Gesellsch.," 1901, vol. xxxiv, p. 2864.
4. Neubauer and Fischer: "Deut. Arch. f. klin. Med.," 1909, vol. xcvii, p. 499.
5. Abderhalden: "Zeitschr. f. physiol. Chem.," 1909, vol. lxii, p. 136.

GRADUATE INSTRUCTION IN MEDICINE*

LOUIS B. WILSON

During the past year I have made a somewhat careful survey of the opportunities for instruction in this country and abroad offered to the graduate student in medicine, particularly in pathology. Without attempting to Flexnerize either the schools or the methods employed, I wish to present for your consideration this evening the results of my observations and deductions therefrom in the hope that they may have some part in shaping the policy of instruction to graduates in medicine by the University of Minnesota.

The graduate physician is notoriously a traveler and a student. That he many times mixes with his studies other pleasures is not, I believe, because he is not sincere in his desire for more scientific knowledge, but because his intimate association with men and women makes him enjoy the humanities without necessarily neglecting his scholastic opportunities. Granted, then, that the medical man is a student and continues to be a student after he receives his degree,—which, after all, is but the State's low-water mark,—what are the opportunities today for him to receive instruction which shall broaden his knowledge, make him a more efficient working unit in the community, and increase his personal enjoyment in his work?

Instruction to graduates in medicine in our country today, it seems to me, is almost in the same state as that of the instruction to undergraduates in medicine of fifty years ago. Most of it is given by the individual teacher where and when and how he pleases. Some of it is given by the organized private "postgraduate" schools, and a very little is given by the great endowed or State medical schools.

---

*Read before The Minnesota Academy of Medicine, St. Paul, Minn., March 6, 1912. Reprinted from "The St. Paul Medical Journal," June, 1912, pp. 287–295.

Instruction by the private teacher has in it many things to commend, and alas! also, many things to condemn. Since the days of Plato men have not found another equivalent for the personality of the truly great teacher. Truth is elusive, most difficult to attain, and yet more difficult to convey to others. The written word, the public lecture, and the class quiz as instruments of transmitting truth all fall far short in efficiency and accuracy of personal instruction by the face-to-face, eye-to-eye, "Mark-Hopkins-at-the-other-end-of-the-log" method. Understanding, appreciation, and inspiration are all thus best conveyed and obtained. But while the effect upon the learner of such personal instruction from the great instructor may be of the best, the retro-active effect upon the teacher himself is apt to have certain unpleasant consequences. The great man is usually not only an egoist, but also an egotist, and unless he is fortunate in having students who not only admire, but also question and even contradict, him his egotism is apt to become sadly edematous. But the development of extreme egotism is, perhaps, not the worst of the faults of the private instruction system. With it too frequently may be developed also selfishness and avariciousness. The laboratory instructor may come to bid for more students who will pay him more fees and the clinical teacher often is found openly or covertly playing for more "referred cases." While "every laborer is worthy of his hire," our highest ideal of the teacher is of one who teaches for the truth alone, regardless of its effect upon the student whose remuneration, either in money or referred cases, he seeks. That teacher who dulls the cutting edge of truth that he may spare the feelings of his paying hearer, or, worse yet, deliberately seeks consultation work by holding back an essential part of his knowledge, has fallen from the high estate of the ideal teacher, and if he be really a man, is ashamed of his frailties.

The private, so-called "postgraduate," school as it exists in

America today is usually an aggregation of second-rate teachers who, having failed as individual instructors, hope, by putting two and two together, to make a hundred. Whatever of personal worth and personal enthusiasm may have been native to the individuals is apt to be overshadowed by the element of avarice which is of a most sturdy growth. Aside from the general mediocrity of the teaching staff, such an institution always contains much dead-and-down timber, which the others must carry, and thus are fomented suspicions, jealousies, and quarrels, the only common ground of agreement being a sincere desire not to train, but to "*skin*" the graduate student. These private "postgraduate" schools are certainly quite as bad as the private medical schools for undergraduate instruction. When they are dead the world will be better off.

The great endowed and State medical schools of this country have hitherto approached the subject of instruction of the graduate student in medicine in a somewhat half-hearted manner. Few of them offer any courses at all and then usually between the sessions of the undergraduate school—a time when the practitioner may not be able to leave his business, or when he should be in attendance at medical society meetings. This has been due in part to the fact that their energies have been devoted largely to increasing the efficiency of their undergraduate work and of keeping pace with the rapid elevation of standards set for the degree of Doctor of Medicine. The change in this regard has been most rapid all over the world and particularly in our own country during the last quarter of a century.

It would seem that now we must have reached almost the limit of the amount of work which may be required of a man before he is permitted to begin the practice of medicine. The present requirements in this State, for example, place the earliest age limit for beginning actual work in his profession at twenty-three years. It would seem that this should not be materially extended. However, to suppose that the medical education of the doctor should stop when he is twenty-three years of age or that the State should cease to be interested in the doctor's development after this period are equally absurd propositions. Indeed, we are coming to realize that we have made a mistake in giving the doctorate degree in medicine at the beginning of a man's career in practice and leaving no honors in medicine proper to be attained by him later. It is unfortunate, for example, that there is no medical equivalent for the degree of LL.D. But while admitting *this* the State should also recognize its incumbent duty to provide—(*a*) for the fullest acquisition of scientific knowledge by trained investigators, and (*b*) the freest transmission of this truth to men already holding the State's stamp of acceptance of them as novices in the art of healing.

Such courses of instruction should be so planned by the great State or endowed institutions as to preserve as far as possible the good points of the system of private instruction, while eliminating its defects. In other words, the individual instructor should come in closest association with the individual student. But the financial relations between instructor and student should be so far removed that the teacher should teach and the hearer should hear regardless of monetary considerations.

The best graduate instruction given in universities today is that organized on the German system. Under this system the teacher receives from the State his commission to teach, accompanied in the higher posts by a relatively small salary, which, unfortunately, he must eke out by private compensation from individual students. He is to only a slight extent independent of the student financially, though quite independent of him so far as his position in the university is concerned. When one sees this system carried to its full fruition in the great clinics of Berlin and Vienna and Paris, he is struck by the development of its defects as well as of its good points. While the accuracy, efficiency, and enthusiasm present are most admirable, the egotism and avariciousness of the instructors are sometimes shockingly apparent. And this is not wholly due to the racial characteristics of many of the occupants of professional chairs. In Denmark and Holland, where the instructor receives the larger share of his compensation from the State and the smaller from the student (in Denmark, for example, all medical education is theoretically absolutely free), one is not impressed so unpleasantly by the teacher's evident desire for paying students, though it must be acknowledged that there the teaching of efficiency as applied to graduate students is not generally so highly developed as in Germany and Austria.

Perhaps one of the best things about the German system is that it prescribes no course, and sets no standard, for the completion of its graduate work. Each instructor may teach what he pleases to whomsoever cares to take his course. The courses are short and adjusted, if possible, to the convenience of the students. They may be found in great variety at almost all seasons of the year except August and early September. The looseness and freedom of the courses accommodates the student and encourages the originality of the teacher, while at the same time it does not harm the community, since the State has already given to these graduates full permission to practise medicine.

The doctor who has started to make a living must usually continue to make a living and cannot leave his business for any long period of time. And perhaps it is best that he should not do so; perhaps it is best that he should take his graduate medical study as he takes his art or his opera—a little at a time at frequent intervals. He thus assimilates and utilizes what he gets with much greater pleasure and economy than he would were he to attempt to gulp down in one dose a sufficient amount to last him the rest of his professional life. With this in view courses in graduate instruction must be short, frequent, and varied. They must permit the practitioner, who can leave his practice for a month only, at frequent intervals throughout the year,—and not in the hot season only,—quickly to get to work and stay at work under a good instructor for the largest amount of time he may take for his professional vacation. At present, the man with four weeks to spend not infrequently wanders about from clinic to clinic, usually watching blood flow or seeing patients already diagnosed and under treatment. How much better it were for him could he find open each month in the year an opportunity to take personal instruction from some great teacher of medicine or surgery who would at the same time be disinterested, either in the student's dollar or in his prospective "referred case."

The general practitioner who wishes to enter a specialty is finding it more and more difficult to do so by merely sending out announcement cards and paying commissions. So many are honestly going in for prolonged special instruction that all are coming to recognize the desirability of it. For this group of graduate students something more than the short course must be provided. To begin with, it is doubtful whether class instruction can be given successfully to such men under ordinary circumstances. They must associate themselves with men noted in the specialty which they aspire to enter. Just here comes in the necessity for laboratory work, particularly in pathology. Most of the specialties in medicine are built upon a basis of a special knowledge of the cause and diagnosis of disease, while skill in treatment comes with practice alone. There can be no question but that the aspirant for surgical honors, for example, should spend some time—a year at least—in the special study of surgical pathology, besides the one or two extra years which he should take in clinical diagnosis and surgical technic. He should thus obtain a basis of fact with which to direct his visualizing of unseen conditions and his plans to meet them. Some opportunity for work of this kind may now be had in this country and abroad, even accompanied by a small monetary remuneration. It would seem, however, that if an institution pays the instructor and furnishes the material and apparatus for such instruction, the student should not expect to be remunerated for the time he puts in, but should, quite the contrary, expect to pay something for the instruction, material, use of apparatus, laboratory service, etc. While the benefits which accrue do go ultimately to the State, they pass more immediately to the student and for them he should pay. It would not seem wise to fix a standard, beyond that already implied in the M.D. degree, for admission to such work or to fix any standard for its completion. The student preparing for a specialty and taking a laboratory course in reference thereto should be encouraged to take adequate time for his preparation, but he should be made to realize that it is up to him to say when, within certain limits, he has had enough. The graduate man should be neither wet-nursed nor spoon-fed.

The graduate student of medicine who seeks further instruction not necessarily for its direct application to the improvement of his own business, but essentially for the pleasure of wresting more truth from nature's storehouse,—in other words, the embryo research man,—is receiving some encouragement in this country and should have more. There is a false conception abroad that the research man is to be sharply distinguished from the practical man. Nothing could be further from the truth. The man who has done one piece of work well, let it be in the laboratory or the shop, has attained a power of observation and of marshaling his facts which will enable him to do any other work better, and the "practical" man is merely the man who observes accurately, decides quickly, and is sometimes right. But it is true that while the research worker does get from his work great personal pleasure, he receives little financial profit, while the community, on the other hand, profits for all time from the result of his labors. This is the real basis for the endowment of research positions.

I do not wish to imply that research positions should be confined to laboratory branches. Endowed fellowships should cover work in the fields of the diagnosis and treatment of disease quite as well as in that of the determination of its causes. But I speak particularly of laboratory work because in that I am most interested.

I have long held that quite as good research work in pathology could be done in any place where material, apparatus, and time offered as in the most popular centers of medical education. The lack in this country is neither the material nor the apparatus, but time. The research man is apt to be in a hurry to accomplish something, and the institution in which he works is apt to want him to get through with it and do something else—teach, practise, or what not. The chief advantage to be derived from going abroad to do research work (aside from its advertising features), is that the student deliberately sets a certain amount of time which he will devote to research and then that those around him let him alone to devote this time to the work which he has undertaken. After a somewhat careful study of the noted laboratories of Europe, I am convinced that if the American student would at home limit himself to the work in hand and permit no one to drag him away from it, he could do quite as good, and in many instances better, work in his own country than abroad. American material is equally good, American apparatus is better, American climatic conditions are less depressing, and American beer is less soporific.

But when the graduate student of medicine does go abroad, I am sure that in many instances he were better served in every way in the laboratories of the smaller institutions like Berne, Freiberg, Heidelberg, Halle, Leipzig, Prague, Copenhagen, or Utrecht than in the great popular clinics of Paris, Vienna, or Berlin. In the latter cities there is an enormous amount of material and there are great teachers, but there are also swarms of students, competition is sharp, and the race is apt to be to the swiftest. The diversions and interruptions of the student's train of thought are here also much stronger in their call than they are in the smaller cities.

The number of teachers and students in the great European clinics and laboratory centers have, however, resulted in the development of a system of organization and management which is well worth investigation by the American visitor. The relations of instructors, fellows, students, and laboratory Dieners show us what will be the probable outcome in this country as we develop more and more our graduate instruction. The latter especially, the Diener system, which is so well developed abroad, we cannot hope to equal here on the same lines. The European laboratory Diener is a trained laborer who, for a small tip, does an enormous amount of routine work for the student who, thus relieved, can devote more of his time to planning and thinking. How we can develop such a system of skilled unscientific labor in connection with our laboratories seems to me to be one of the most profound problems before us, and one which we must solve that our graduate students may not be turned into Dieners rather than scientists.

In this connection I wish to say just a word concerning information which may be had by the American medical student going abroad. One of the most interesting books for such a student to read is Professor Ralph Thompson's "Glimpses of Medical Europe." A more recent work, and one more professedly a hand-book, is Honan's "Hand-Book to Medical Europe." This is very complete so far as Berlin and Vienna are concerned, but for most of the remainder of Europe, particularly of Holland and the Scandinavian peninsula, it is so incomplete and in some instances so inaccurate as to give the prospective student not only an inadequate but a false idea of the work which may be seen in these countries.

Before leaving the discussion of European laboratories I may say that while one finds many things to commend and admire in the laboratories in the British Isles, there is nothing there so superior to our own laboratories in material, equipment, or organization to warrant one spending much time in them.

After this brief consideration of the conditions as they now exist, what recommendations may be made for their betterment in this country? So much depends upon local conditions that one must confine one's self to those with which he is most familiar. At Rochester, where all our work is related to surgery, the present laboratory staff is fully engaged in diagnostic and research work. Some opportunities are afforded the men who desire to do research work in the shape of three or four positions, which are the equivalent of annual fellowships. We have frequent requests from men who wish to come to our clinic for a few weeks' work to aid them in their general practice, from a few who wish to come for two or three years' work as a preparation for a surgical career, and from a very few who wish to come for research work pure and simple. Our room and facilities are at present too limited to permit us to take in men, except as observers, who can stay but a few weeks. Besides the surgical clinic, which usually occupies the visitors' time in the forenoons, there is given each afternoon a diagnostic clinic, and three evenings a week a lecture by some member of the staff. In the laboratories men who come for a short visit only are treated as welcome visitors and not as students. It is difficult to see how we can do more than this at present. Were our institution connected with the university, short courses, say, of one to three months' duration, in surgical pathology might be given in connection with a more general course offered by the University to graduate men. Were such a course offered it would seem wise to repeat it, say, every three months, and even were there men enough to be taught in classes, each student should still be permitted to select, as far as possible, his own problem.

Students who are preparing to enter the field of surgery and who may give a year to surgical pathology can now be accommodated in limited numbers at Rochester as volunteers. The facilities in this department we hope materially to increase in the near future. These men have an opportunity to study the pathologic material of the clinic, both from the diagnostic and research standpoints. Such a course, if combined with two years of clinical and operative experience, furnishes a good training for men preparing for a surgical specialty.

Our research positions are limited in number and are held by men who are giving from one to several years to studies in pathology.

It would be presumption on my part to offer to those who are much better acquainted with the institution than am I suggestions for instruction to graduates in medicine by the University of Minnesota. It would seem desirable, however, that the University should aim to provide in its laboratories, in its hospitals, and in its clinics generally, first, for graduates in medicine who have a few weeks to spend; second, to a much less degree for the men who are preparing for a specialty; and, third, to a much greater degree for the men who wish to do research work. If the University of Minnesota can find itself able financially and otherwise to give short courses at frequent intervals on the subjects which these three classes of graduates in medicine demand, it will prove a good thing not only for the student, but also for the instructors and the institution.

A SHORT VISIT TO SOME OF THE HOSPITALS IN GERMANY, AUSTRIA, SWITZERLAND, AND HOLLAND*

WILLIAM J. MAYO

Since my former visit to Germany conditions have changed markedly: there is less of the military and more of the commercial. What has been the effect in Germany of the present commercial era upon science? Many Germans deplore it and believe that commercial success has become the German ideal, and that science, literature, and art are not in keeping with the best traditions of the last generation. During my recent visit I saw no reason for pessimism so far as surgery is concerned. The great German clinics are in the hands of keen, well-trained, and ambitious men, and there is a large output of new and good things. One has but to remember the recent contributions to surgery of the chest, head, abdomen, bones, and joints to recognize the great position of German surgery in this generation.

The German hospitals are large, well organized, and efficient. Trained women nurses are now in charge of the nursing in all the hospitals of note. The support of these hospitals comes largely from compulsory insurance, which is demanded of both employe and employer, and the municipality and the state furnish their proportion of the funds.

German hospitals are usually built in the one- or two-story pavilion style. The one in Hamburg and the new Virchow Hospital in Berlin, the two largest, are of the one-story, separated-pavilion type, laid out in streets. In the Hamburg Hospital there are nearly 100 buildings with 2600 beds, and the Virchow, with

---

*Reprinted from the "Journal-Lancet," August 15, 1912, pp. 423–427.

2000 beds and 1000 employes, has about 60 buildings. The objection to this type of hospital is the expense of operation, the difficulty of keeping the food warm, and the necessity of transporting patients out-of-doors from the operating buildings to their respective ward buildings.

Considered from the standpoint of economy of operation, I believe the best type of hospital to be the four-story connected-pavilion plan, such as the new hospitals at Vienna and Munich.

To a certain extent the German surgeon is relieved of direct responsibility to the patients, and he concerns himself with the pathologic processes rather than with the patients' likes and dislikes. This has its good features, inasmuch as the surgeon's hands are not tied by the prejudices of patients and their friends. It permits greater liberty in dealing with the individual patient, and the German surgeon has a correspondingly high sense of responsibility in not taking advantage of this fact to apply methods of treatment which are still in the experimental stage.

HAMBURG

The surgical clinic at the Ependorf Hospital is divided between Professor Kümmell and Professor Sick.

Our visit to Professor Kümmell was most interesting. He allows his patients to get up the day following an operation and believes this hastens convalescence. Ether, in 5 per cent. salt solution, given intravenously, has been used as an anesthetic in this clinic in more than 140 cases without accident. We witnessed one operation under this anesthetic. Professor Kümmell says that thrombosis will not follow the administration if salt solution be passed through the needle continuously before and after the ether solution. In place of iodoform gauze he uses 20 per cent. neoform gauze, which is non-toxic, non-odorous, and quite as efficient.

In one case of traumatic epilepsy, after an osteoplastic flap was turned from the parietal region and the dura was excised, Professor Kümmell transplanted a piece of the fascia lata with considerable fat attached to cover the cerebrum—fatty side next to the brain tissue. He said he had used this method in a number of cases. An electric saw of his own device was used to open the skull.

A nephrectomy for tuberculosis was made through a lateral transverse incision. The cut end of the ureter was touched with iodin and brought out of a stab-wound through the skin so that if any infection in the ureter followed, it would pass outside of the wound. Professor Kümmell impresses one as being a lover of truth in science, is original in his methods, and is a splendid surgeon.

Unfortunately, I did not see Professor Sick operate during this visit, but I had the pleasure of attending his clinic for some days ten years ago. He is a master surgeon and has a large amount of surgical material.

BERLIN

Berlin is the imperial city of continental Europe—forceful, aggressive, and competent. Professor Bier is here, the leading spirit in surgical progress. He is intensely interested in his work, and his clinic is very popular, especially with the American student.

Bier uses the congestion treatment for tuberculosis of joints, seldom resecting. He sometimes resects the stiffened tuberculous elbow, since it gives motion after a fascial transplantation. I visited three of his wards, filled with patients with tuberculous joints undergoing congestion twelve hours at a time each day. Some of these patients certainly showed marvelous improvement. I speak of this because, at the present time, the Bier treatment is quoted but little.

Bier uses local anesthesia, if possible, with novocain, 0.5 per cent. He does not often use spinal anesthesia, being so well satisfied with the local. I witnessed the removal of a kidney under local anesthesia. A fracture and paralysis of the ulnar nerve were operated on under conductive anesthesia of the cervical plexus, and an osteomyelitis of the tibia under local vein anesthesia through the internal saphenous vein below a rubber constrictor of the thigh.

In Schede's resection of the chest-wall, after dissecting the skin-flap, Bier uses a saw to cut through muscles, bone, and pleura, thus preventing hemorrhage. Catgut is used for sutures and for ligatures.

Professor Bier has the largest surgical clinic in Germany, and he is a worthy successor to Langenbeck, Dieffenbach, and von Bergmann, who, each in his time, were the leaders of German surgery.

Körte, of Berlin, is a painstaking, conservative surgeon, who enjoys the respect and confidence of his confrères. He is one of the best general surgeons in Europe, and his material is good. In operating on the gall-bladder he makes a curved incision along the chest-wall to avoid injury to the nerves and possible hernias later, and, as a rule, he prefers cholecystectomy to cholecystostomy. He makes the posterior one-stage operation for rectal cancer. In intestinal anastomosis he uses end-to-end union in the small and end-to-side union between the small and the large intestine. Catgut is used for ligatures. Körte frequently employs resection for tuberculosis of the joints and, so far as I could learn, prefers this to prolonged mechanic treatment in most cases.

At the Charity Hospital, Franz is chief of the obstetric and the gynecologic clinic, and he has a large amount of work. I witnessed several of his operations, and have never seen more skilful pelvic surgery. A complete abdominal hysterectomy for cancer of the cervix was a masterpiece. Franz makes the transverse abdominal incision of Pfannenstiel, and uses spinal analgesia; this was the only clinic in which I saw it used.

The American Medical Association of Berlin has good quarters, library, etc. American physicians visiting Berlin may obtain here valuable time-saving information regarding Berlin clinics.

Prague, in Bohemia, Austria, is a city of about 600,000. There are two universities here, one German and one Bohemian, each having a complete medical department. Schloffer is chief surgeon in the German University Hospital, coming to Prague from Innsbrück. He was formerly an assistant of Wölfler, who was chief of the Prague clinic for many years. Schloffer is a man in early middle life, a splendid surgeon of the sound conscientious German school.

The Bohemian University Hospital is an equally fine institution, and has had associated with it many distinguished men. Maydl, made famous by his operation of transplantation of the ureter into the rectum and for a simple method of colostomy, was formerly chief surgeon. Kukula is the present chief surgeon. He has traveled extensively and has had a distinguished surgical career. The second position in surgery in this university is held by Professor Jedlicka, a fine surgeon and a charming gentleman, to whom I am indebted for a most pleasant and profitable visit to Prague.

The gynecologic clinic in the Bohemian Hospital is under the direction of Professor Pawlick. I was so fortunate as to see his associate, Professor Pichad, do some very fine pelvic surgery.

The eye clinic in the German University and the orthopedic clinic in the Bohemian University have a reputation over all Europe and they have a wealth of material.

VIENNA

The general hospital in Vienna has been described so frequently in detail that I can add little of interest. This great hospital of 2600 beds is old but still useful. A new and modern group of buildings in close proximity is now under construction, and several departments are completed. Vienna may be said to rank easily first as the world's medical center, on account of the vast amount of material for study conveniently located at this hospital. The conditions here are ideal for students as contrasted with many hospitals in Berlin and other cities where much time is lost in traveling about from one hospital to another.

von Eiselsberg, whose reputation, so justly earned, needs no words from me, is the chief surgeon of the first division of the surgical department of the University of Vienna. Precision, thoroughness, and splendid asepsis are characteristic of v. Eiselsberg's work. He is kind and conscientious in his treatment of patients, and he is a great teacher of surgery. I was so fortunate as to witness a number of his operations covering a wide range of work. All were done with equal facility and skill. I also had the pleasure of going through the wards and seeing patients doing well following operations.

Dr. Clairmont is Professor v. Eiselsberg's first assistant and is a surgeon of great ability. He has visited America and is well known here. It was exceedingly interesting to see the two operating-tables in simultaneous use in one operating-room, one by Professor Eiselsberg and the other by Dr. Clairmont. The technic and methods were identical, and each was demonstrating to an interested group of spectators. This clinic should be visited by every American surgeon traveling in Europe.

The second surgical clinic is under Professor Hochenegg. I was greatly interested in his operation for cancer of the rectum, which has deservedly given him a great reputation. He has done about 240 operations by his method, and his assistants have done as many more, making about 500 cases—a unique experience in one clinic. The Hochenegg operation for cancer of the rectum is of the Kraske type, *i. e.*, removing the fourth and fifth sacral vertebræ and the coccyx, and in two-thirds of the cases making a sacral anus. In about one-third of the cases the bowel is drawn down through the anal muscles or sutured in continuity. In the 500 cases operated on, the average mortality was between 18 and 19 per cent., with 20 per cent. of five-year cures. In his private work Hochenegg's mortality is a little under 10 per cent.

At the Rothschild Hospital I saw Professor Zuckerkandl operate on three kidneys, making a transverse incision in the lateral position. Professor Zuckerkandl is famous for his contributions to renal surgery. I found his work most interesting and instructive. Those interested in surgery of the kidney should attend his clinic and study his specimens. Dr. Bachrach is Professor Zuckerkandl's first assistant, and Dr. Jeriselum his junior assistant. Both have visited America.

Professor Wertheim has charge of the second gynecologic clinic in the Vienna Hospital. I was present while he performed the operation which bears his name for radical cure of cancer of the cervix by the abdominal method. The pelvic glands are not removed unless enlarged, and the ureter is not separated from its bed more than is necessary, because of the possibility of fistulæ in the ureter following such disturbance. He devotes great attention to the tissue immediately about the cervix and upper vagina. In my experience, this is correct in principle. Wertheim is a persistent, thorough operator, and gives one the impression that he knows exactly what he is about. He has operated on more than 500 cases with an average mortality of 14+ per cent. and has had 24 per cent. of five-year cures. I visited his wards and was shown some cases of ureteral fistulæ, also a rectal and a vesical fistula following operation. He said they were patients on the frontier between the operable and the inoperable, but he felt it his duty to operate upon them, since they might be cured. I have no hesitation in saying that the Wertheim operation as performed by him is the best operation for cancer of the cervix that I have seen.

Professor Schauta has charge of the first gynecologic and obstetric clinic. Six hundred patients with cancer of the cervix have been operated on in this clinic, with a mortality of 6 per cent. and about 20 per cent. of five-year cures. Schauta makes a very extensive vaginal hysterectomy; the ureters are exposed and separated by using the Schuchardt vaginal and perineal incision. Through the kindness of Dr. Christofoletti, Schauta's first assistant, I was enabled to see an excellent demonstration of the method in a difficult case. There are few complications following this operation, and I believe it to be a thoroughly good one. In my opinion the Wertheim method enables wider and more thorough extirpation, but it has a higher mortality and incurs greater danger of secondary complications. Whether the advantage to the patient in the Wertheim method is sufficient to overcome the difference in difficulty, danger, and complications, is an open question.

Vienna may be said to be the favorite city of American medical students. It has an American Medical Society similar to the one in Berlin, with an average of 120 members enrolled. I was present during an interesting meeting of the Society. An American physician visiting Vienna will do well to visit the American headquarters, where he will be quickly put in touch with medical Vienna.

BERN

For thirty years the Kocher clinic at Bern has been one of the leading surgical clinics of the world and is still one of the leading clinics. More new and good ideas have come from this one clinic than from any other of my acquaintance, all due to the genius of one man, Theodor Kocher, who is still vigorous with a seemingly perpetual youth. Kocher is constantly at work trying out new things and improving the old. He is an inspiration to surgeons the world over. The work in this clinic is marked by the extensive use of local anesthesia, by painstaking care in handling the tissues, and the exclusive use of silk for sutures and ligatures. Kocher is a great believer in the early operation for exophthalmic goiter and says that delay is unwise and leads to organic degenerations from which the patient may never recover. I was greatly interested in his method of procedure for prolapse of the uterus, which he has practised for many years. The abdomen is opened and the uterus drawn up into the abdominal incision, the entire uterus above the cervix being made subcutaneous; the muscles are sutured to the uterus just below the fundus. If the operation be performed during the child-bearing period, the Fallopian tubes are dissected out. I had an opportunity to examine several cases following operation.

TÜBINGEN

The surgical clinic at Tübingen is under the direction of Professor Perthes, a former assistant of Professor Trendelenburg. The hospital is very well appointed, the operating-rooms are well equipped, and the organization for the surgical work is of the best. Tübingen is a small city, of less than 20,000, and is typically a German university town. There are 2000 students in the various departments of the University, which is the only one in the entire province of Württemberg.

In operations on the gall-bladder, Perthes makes an incision beginning at the ensiform cartilage in the midline to a point one inch above the umbilicus, then cuts the right rectus across, and extends to the right as far as necessary. The exposure is fine, and no hernia follows. Perthes usually does cholecystectomies because the patients come late. He does considerable work in surgery of the lungs, and demonstrated many interesting cases. I would advise all American surgeons visiting Germany to attend the clinics at this university. We saw in Tübingen much that was new and interesting, and I enjoyed my stay there very much.

BONN

Bonn is an old university town of great renown and has over 4000 students, 600 of whom are medical. The surgical clinic has always been under the directorship of a great surgeon. Trendelenburg was here before he went to Leipzig; Max Schede came from Hamburg at the height of his justly earned reputation and died here. Bier was here before he went to Berlin. Garré is now in Bonn, and is in every sense a sound and forceful surgeon. The organization and the discipline of his clinic are nowhere excelled. There is literally "a place for everything and everything in its place." Garré is one of the best teachers of surgery to be found in Germany, and he operates, not only on patients at the clinic for his students, but also on the cadaver. Like so many continental surgeons, he uses silk exclusively for ligatures and sutures, always fine and out of a bichlorid solution. He says the advantage of using silk is in its fineness, its sterility, and its complete impregnation with an antiseptic.

HOLLAND

There are four universities in Holland, the oldest at Leyden. The two principal medical schools are located at Amsterdam and Utrecht. The Municipal Hospital at Amsterdam has about 600 beds, 200 of which are surgical. It has two divisions under the supervision of Professor Rotgans and Professor Lanz, both of whom I had the pleasure of meeting. Professor Rotgans is a very active surgeon and a good pathologist and diagnostician. I witnessed a number of operations in his clinic, one, a multiple pancreatic cyst of large size in a male patient, was most interesting, since a correct diagnosis had been made before the operation. Professor Rotgans has used the anterior method of gastrojejunostomy with good success for many years, and he prefers the method in all cases.

Professor Lanz is not only a most capable surgeon, but one of the foremost art critics in Holland. He is one of the controlling spirits of the National Gallery of Art in Amsterdam. He has a large private hospital in which he makes provision for the care of the poor, as well as the rich, and especially for the people in moderate circumstances. The middle classes on the Continent are usually forced to the public clinic, or they are financially embarrassed in the private ones.

UTRECHT

The States Hospital in Utrecht is new and modern in every respect, and is an excellent hospital to visit. There are 120 surgical beds, and about 1600 operations are performed a year. Professor Lamieris is the directing surgeon of the clinic and the professor of surgery in the University. He is progressive in his work, full of enthusiasm, and an excellent operator. He performs the operation for indirect inguinal hernia by a simple and effective method of his own. He incises the canal, removes the sac, ties high, and drops back, merely placing three or four sutures in the cut aponeurosis. For direct hernia he uses the Bassini operation.

The Dutch trained nurses are strong, intelligent, capable, and neat and clean in appearance. I have seen no better.

There is a distinct school of German surgery, and, so far as I know, it is the only distinct national school, although we have a standardization of technic in America and a trend of surgical opinion which may be said to be American. The American school has been greatly influenced by German ideals and German methods. The American travels and learns, and America is the surgical clearing-house for international surgery. German surgery is forceful, thorough, and exact, but has not been influenced by foreign ideas to any extent. German surgery dominates the neighboring countries, and all the clinics I visited this year were distinctly characteristic, whether in Germany, Austria, Switzerland, or Holland. The central idea is based on the sense of sight. "To do your work well," says the German, "you must see what you do"—hence large incisions. To the American these incisions may seem excessive, yet we all know the size of the incision does not often affect the end-results. Another important point in German surgery is to eradicate the disease, if possible. Operations are not, therefore, undertaken lightly; the punishment must fit the crime, and, with the exception of cancer, patients are operated on in a more advanced stage than with us. All the gall-bladders which I saw removed should have been removed; they were functionless because of their advanced pathologic condition. German surgery deals with pure science; sentiment has no place in it. The directing surgeons of the clinics are responsible men, well trained and effective. They have three missions to perform: (1) To advance surgical science; (2) to teach the next generation of surgeons, and (3) conscientiously to devote themselves to help their patients.

The German of today is the most potent factor in continental Europe. Every child in America should be taught the German language.

OBSERVATIONS ON GERMAN SURGERY*

CHARLES H. MAYO

During the past summer it was my privilege to make a most instructive and enjoyable visit to some of the renowned clinics of Germany.

The 25 university centers in Germany seem to be classified according to equipment, wealth, numbers of students, and extent of population. As opportunity arises, the chiefs of clinics are advanced in the scale of appointments or they pass on to other universities and higher positions. The better of the first assistants are chosen to fill the vacancies.

The hospitals are large and complete as to equipment, usually occupying a space of about four of our city blocks. The large park-like grounds, with plenty of air and sunlight, make ideal surroundings for the hospital buildings, which are usually constructed on the pavilion system. The location of hospitals in Germany is in marked contrast to that in our own country, where hospitals are often built in the business centers, without ground space, as modern skyscrapers, with the discomforts of heat, smoke, dust, and noise—air and light being secondary considerations.

The Virchow Hospital in Berlin has been constructed recently, and is a model in detail. However, in Frankfurt-on-Main is one of the best-equipped and most modern hospitals that we visited. It has been remodeled from an old institution. Rehn is the chief surgeon here, and has a large clinic.

The hospitals are all well equipped with modern Röntgen apparatus, and this department of diagnostic work seems to have been developed to a wonderful degree of perfection. In Frankfort we saw excellent radiographs taken in $\frac{1}{200}$ of a second. The work of Haudick, of Vienna, in the reading of the radiograms and in the interpretation of fluoroscopic pictures in cases of gastrointestinal diseases, has occasioned much interest.

---

*Read before the Western Surg. Assoc., December 20, 1912. Reprinted from the "Journal-Lancet," March 1, 1913, pp. 134–137.

A great deal of care and thought has been given to the arrangement of the operating-rooms, and especially to the lighting system, several of them having the so-called Jena system, with light from a powerful arc focused onto mirrors. In some instances these mirrors are fixed and in others they can be tilted. There is considerable water in evidence in most of the operating-rooms, but, on the whole, they are much drier than during the antiseptic period of surgery. In most of the clinics the immediate site of operation is prepared by the benzin and iodin method.

The surgeons are exceedingly well prepared for their work. They have served long apprenticeships, and they all take pride in speaking of the well-known men with whom they studied and served as assistants. They are especially well informed concerning the world's medical literature. As a rule, they may be said to take themselves and their work rather seriously, and impress the fact upon others. Very few of the surgeons change their clothing before operating, often taking off but the coat and vest, slipping on a rubber gown, and drawing a pair of short rubber boots over their footwear.

In all the operating-rooms are a great many assistants, and after the essential details have been carried out by the master surgeon, the case is passed on to the first, second, and third assistant surgeon, who completes the work. In Bier's clinic in Berlin, which is one of the largest in Europe, we counted 27 persons—surgeons, interns, orderlies, and nurses—engaged in operating on or completing the work on three patients at one time. There was opportunity to visit but three of the general surgical clinics in Berlin, which were conducted by Bier, Hildebrand, and Körte. We also visited the clinics of Bumm and Franz, which are devoted to gynecology, and that of Krause, who specializes in the diseases of the brain and nervous system. He is also doing much general surgery.

The excellent team work of those engaged in diagnosis in all the departments is worthy of note, each diagnostician taking great pride in the part he plays in the making of a diagnosis. He follows his cases to the operating table to witness the conditions found on exploration. In abdominal surgery much time is given to make an exact diagnosis, rather than the diagnosis of a surgical condition, and the operation is carried out strictly with reference to this.

Very little general exploration is done, although the incisions for abdominal work are generous ones, permitting ease of investigation and manipulation. Such incisions do not appear necessarily to lead to a long confinement in bed. The period of convalescence has been greatly shortened, particularly in Kümmell's clinic in Hamburg, who has most of his patients not previously bedridden up for a few minutes the day after operation, and for an increasing period each day thereafter.

Franz, of Berlin, an exceedingly clever operator, makes use of the transverse or Pfannenstiel incision in abdominal cases, and secures a good exposure after a vigorous stretching of the incision. He favors spinal anesthesia.

Many cases of diseases of the stomach are to be seen in all the clinics, and a correct diagnosis of the condition is the rule.

Ulcers are often treated by resection of a complete ring of the stomach, including the ulcer. The two portions of the stomach are reunited, and a posterior gastro-enterostomy is made when there is interference with the drainage of the stomach.

In carcinoma of the stomach partial gastrectomies by the Billroth No. 2 method are common operations, although Hofmeister, of Stuttgart, uses a modified Billroth No. 1 by attaching the jejunum. He protects the fatal point of union of stomach and jejunum by continuing the suturing of the small intestine over the suturing of the stomach, the jejunum being brought through the mesentery of the transverse colon to which the anastomosis is attached by sutures at the close of the operation.

They have evidently had but little trouble in German clinics from hernia of the small intestine through the opening in the transverse mesentery of the colon following gastro-enterostomy for ulcer, since rarely did we see sutures applied to prevent the possibility of this accident.

Free use is made of the Pagenstecher linen silk or catgut suture material, some of the surgeons making an anastomosis in a very few minutes with a single row of interrupted mattress sutures of catgut or silk; others, however, use the double row of sutures with the third row posteriorly for a more careful control of hemorrhage.

Bumm, in Berlin, and Wertheim, in Vienna, make complete abdominal operations for cancer of the uterus. In Schauta's clinic a perineal operation was apparently just as radical, a very large exposure being made by a lateral vaginal incision. It is generally admitted that when the disease has advanced outside of the uterus with glandular involvement, the percentage of five-year cures is small indeed, and that delay in the continuance of growth (I do not call it recurrence) depends largely upon the resistance of the individual. The somewhat increased mortality necessarily following tests the best judgment of the operator in deciding how radical a procedure is warranted in these advanced cases.

Many operations on the gall-bladder and ducts were seen in the various clinics. Most of these cases are operated on somewhat later, on the average, than in this country, which undoubtedly has led to the higher percentage of cholecystectomies being done there than here. Perthes and Payr use a modified Kocher incision, which gives a fine exposure of the ducts. The incision extends from the ensiform cartilage to the umbilicus, and from the umbilicus at a right angle as far as the costal margin if needed. The rectus muscle is divided after being sutured to its sheath in two rows lateral to the proposed incision to prevent retraction.

An interesting point in the causation of gall-stones has been worked out in Payr's clinic in Leipzig. He shows that the percentage of cholesterin in the bile of pregnant women is four times as great as in other women or in men, and, as 19 per cent. of the weight of the gall-stones consists of cholesterin, he believes this accounts for the fact that such a large percentage of the cases of gall-stones occur in women, and that the first symptoms have become manifest in the majority of them during pregnancy or shortly after.

In three instances Wilms has made an anastomosis of the hepatic duct and duodenum with a permanent rubber tube. The first case was done three years ago. He presented two of the patients at the clinic.

German surgeons have a great liking for reconstructive work, and much can be learned in a study of their bone, joint, and plastic surgery. Lexer, of Jena, showed a number of cases in which he had transplanted the entire knee-joint immediately removed from amputated limbs to replace ankylosed ones. A very useful degree of motion was present in the several cases shown. Payr is making resections of fixed joints to secure motion after Murphy's original plan, removing more from the femur than the head of the tibia, however, which is the reverse of the present method. He transplants the fascia lata and its fat into the joint in the same manner. In the end-results of the operation the radiogram shows but little difference between the methods, both permitting of a near function from like changes in the different tissues.

A very common plastic operation is that of transplanting fat to fill out defects of the skull and the face, as well as the free use of transplanting the fascia lata with the fat side down in operations on the brain, especially in epilepsy, the dura over the exposed area being entirely cut away. Perthes transplants hernial sacs, removed at operation for this purpose, into ankylosed joints. They claim greatly improved results by such methods and have much less trouble from adhesions and cystoid scars than followed former operations upon the brain. Hildebrand decompresses by aspiration of a ventricle through the corpus callosum. The skull is opened with a small drill.

In three clinics we observed an artificial esophagus made of a section of small intestine. They were connected with the stomach, extending over the sternum beneath the skin and continuing on to the neck as a tube lined with skin, which was connected with the esophagus, three operations being required. Lexer's case was the only completed one, and it was interesting to see the bolus of food go sliding down through this artificial esophagus over the front of the chest. In all the cases the stricture was non-malignant. Enderlen, in a similar case, united the esophagus with the stomach, which was drawn through the diaphragm. The patient died on the eighth day of pneumonia; the autopsy did not show any infection; healing of union was perfect.

He also reconstructed the alæ of the nose with the lower lobe of the ear, and exhibited many bone and joint reconstructions.

Perthes, of Tübingen, and Wilms, of Heidelberg, showed many cases of surgery of the lung, especially partial removal of the rib in tuberculous conditions, to place the lung at rest. The advantage claimed over the Friedreich operation by the removal of short sections of several ribs, front and back, through several incisions was the slower shrinking of the wall of the chest. They use differential pressure in interior operations on the chest.

Bonn is a most interesting university center. Professor Garré, one of the best surgical teachers of Europe and an operator of excellent judgment, is in this university. Professor Makkas presented a patient in the clinic with exstrophy of the bladder in whom, three years before, he had devised a bladder from a cecum, which was separated from the colon after making an ileocolostomy. The ureters were connected with it, and the bladder formed was drained every three or four hours by a catheter passed through the lumen of the appendix, which had been converted into a urethra by an appendicostomy, However, in the radiogram just taken the ureters showed dilatation extending to the kidney.

Goiter is a very common disease in Germany, and operation for the malady of frequent occurrence. The methods of operation are similar in plan in all the clinics—transverse incision, double ligation, and division of all the tissues over the thyroid gland, very careful ligation of the arteries with some strong material. Few surgeons trust catgut for this purpose, and use silk, linen, or silkworm-gut. In Germany exophthalmic goiter is considered a surgical disease, and it was interesting to see so many cases in the various hospitals. Preliminary ligations of the arteries are made in most of the clinics when the disease is operated on in an active stage. Rehn now removes one lobe of the thymus gland, if found, with the extirpation of the thyroid. Most excellent results are obtained by operation, and the mortality is reduced to a very low percentage. The surgical treatment and the results are borne out by the work of their physiologists also.

A general knowledge of the development, function, and therapy of the various ductless glands of the body seems to have been worked out here with much less bias or theory than in other countries.

In Leipzig a most interesting visit was enjoyed with Professor Trendelenburg, a well-remembered visitor to America, now retired from active practice. Here also Professor Tillmanns showed some interesting cases at the Children's Hospital. Many varying tuberculous lesions were being treated with tuberculin, to which was added the staphylococcous toxins. The patients showed marked improvement, claimed to be due to a more active local inflammatory reaction.

In Frankfort-on-Main an interesting visit was made through the laboratories of Paul Ehrlich, one of the foremost men in the profession today. He is a small, active, jolly fellow, most interesting to meet, and a typical scientist.

In Vienna the average attendance of American surgeons at the clinics is about 150. They maintain a continuous local society, deriving inspiration from the excellent surgery of von Eiselsberg,—a student of Billroth and a clean-cut surgeon,—Hochenegg, Clairmont, Zuckerkandl, and others of world-famed surgeons and clinicians of that city. The atmosphere of the clinics is quite American.

The details of anesthesia varied in the different clinics. As a rule, the operating-rooms are supplied with an apparatus which delivers to the patient oxygen, ether, and chloroform in exact proportions. Körte, in Berlin, was using the old A. C. E. or Billroth mixture. He claimed that ether alone presented some difficulties when used upon those patients who were accustomed to their "Schnapps." While noting the excellence of general anesthesia as produced by the various methods (ether as a drop method is used much in Vienna), we were impressed with the wonderful development of the various methods of local anesthesia that have been perfected in the several clinics. One could not but feel that there had been some necessity for it, owing to trouble in the past with general anesthesia. The best local anesthesia resulted when twenty to thirty minutes were allowed to elapse between the injection and the operation. Abdominal operations of all kinds were made under intradural spinal anesthesia. The skull was opened and an operation on the brain was made under local anesthesia. The middle and posterior branches of the fifth nerve were injected at the base of the skull, and in some instances the ganglion has been reached with a curved needle, permitting of most extensive resections and other operations on the face and jaws. Operations on the limbs, bones, and joints were made by brachial plexus and sciatic nerve injections of novocain, the nerves being found by an insulated electric connected hypodermic needle. They use the pneumatic tourniquet of Perthes, distended within a metal shield, which gives perfect control of circulation, and is somewhat similar to the apparatus used by Bunts of Cleveland.

Kümmell made a partial gastrectomy and gastro-enterostomy, using 5 per cent. ether in salt solution, given intravenously in the arm. A continuous stream of ether was introduced when needed, and salt solution when anesthesia was sufficiently deep, 16 to 18 grams being used during the operation. Evaporation probably reduces the strength of this to about 3 per cent. when received by the patient.

Prostatectomies and operations for hemorrhoids were made by an extradural spinal injection each side of the sacrum and coccyx. Wilms made rapid perineal prostatectomies—one in three minutes and another in four minutes, using a long needle and deep injections of novocain about the base of the bladder and prostate, the needle being inserted through the perineum with the finger in the rectum as a guide. A number of herniotomies were made by the Heinrich-Brown method of local anesthesia—four deep penetrations of the needle and injections of novocain beneath the aponeurosis, each two inches lateral to the ends of proposed incision, with local skin injection along the line of incision.

A case of osteomyelitis of the tibia in a fourteen-year-old boy was operated on after securing anesthesia by opening the saphenous vein in the thigh below a tourniquet and injecting it, under tension, by a syringe filled with novocain solution.

All these methods showed to what an extent an operation can be carried out successfully without the use of general anesthesia when it is contraindicated.

German surgery can well be spoken of as a "school of surgery," and has more or less dominated the surgery of the world. The German surgeons are most efficient. While their surgery has originally developed almost entirely from the laboratory side, the clinical work today has certainly been advanced remarkably. The methods of hospital development, support, and control have created a system which is adapted to the masses in contrast to that in this country, which considers the individual. Although many of their methods are not adapted to our institutions and people, they are well worth consideration by our surgeons, since there is much to be learned from them.

ADDRESS, FEBRUARY 10, 1912

WILLIAM J. MAYO

As one of Dr. John E. Owens' many friends, I am glad indeed to felicitate him on the completion of his fifty years of hospital service, and to wish for him a long service in the future. He has earned a rest, but I know him too well to believe he will take it, and some of us who are here tonight may again greet him on the completion of his seventy-fifth year in St. Luke's Hospital.

Dr. Owens has justly won a distinguished place in the history of modern surgery, and his name will be among those who have made American surgery what it is today. Too often it happens that men who have played a great part in the development of the country have never known that their work was recognized and appreciated—they have not known the kindly feelings entertained for them by the people. Oliver Wendell Holmes, in speaking of the life of the doctor, pointed out how little he could expect in the way of financial reward, that his statue never adorned the walls of the halls of fame, and that the most he could expect would be to have some loathsome disease named after him.

Belonging as I do to the younger school of surgeons, I can only go back some twenty-five years in my personal acquaintance with Dr. Owens. His early work in Rush Medical College was before my time, and can be better spoken of by some of the older men present who were contemporaneous with those events.

I remember well the first time I met Dr. Owens; it was in the year 1886, when I went to Washington as a visitor to attend the meeting of the American Surgical Association—a most momentous occasion to me. There were present from abroad at this meeting Thomas Bryant and John Erickson, from England. I still remember my pride in the five western surgeons who were present: Dr. John E. Owens, Dr. Edmund Andrews, Dr. Moses Gunn, Dr. Charles T. Parkes, and Dr. Christian Fenger. These men were foremost in the debates, and in that early period the work of these men from the West was taken into serious consideration by surgeons the world over.

In making standards of comparison, a surgeon should be estimated, first, as to his ability to care for the patient; second, as a teacher of students; third, as a contributor to surgical literature through the printed page.

Dr. Owens is a good surgeon from the standpoint of the patient; safe, sound, and conscientious, his attitude is essentially that of the great English surgeons. In making ward rounds with him I learned one thing which I have never forgotten, that is, the beneficial effect of assured composure and a cheerful demeanor in quieting patients and giving them courage and hope. With a cheerful countenance and a little joke he went from one bed to another, leaving behind a smiling, encouraged patient.

Dr. Owens is a great teacher. I have often heard my brother say that in his college days Dr. Owens' lectures and clinics were not only thoroughly enjoyed, but remembered. These lectures were based upon a large personal experience, and contained characteristics not easily forgotten. "Knowledge is that which we learn from others: wisdom is that which we already know"—as a teacher, Dr. Owens was wise.

Dr. Owens' contributions to surgical literature have always been judicial in character, exhibiting a soundness of judgment which has made them most instructive. I was a little curious to know the extent of his contributions to literature within the period of my acquaintance with him, and I found some 20 odd papers and discussions of such importance that they were indexed for reference.

Dr. Owens may justly be called the originator of modern railway surgery. Up to his time the medical departments of railroads were developed along three different lines: first, political considerations; second, considerations as to the value of the physician as a legal witness; third, and least considered, the physician's ability to care for the injured of the road. Speaking for the Northwestern, I have never known an appointment to be made by Dr. Owens which had either political or legal significance; every man secured in the capacity of surgeon was chosen on his merits, as well as his standing in the community in which he lived. Neither his politics nor his ability as a medical witness had any weight with Dr. Owens in making the appointment.

Dr. Owens' relations with the surgeons of the railway have always been most friendly. He has ever been ready to help and advise, and has established an *esprit de corps* which is worthy of emulation by all similar organizations. The changed attitude within the past ten years in the surgical department in the railway service of America has been due more to Dr. John E. Owens than to any other man or group of men in the medical profession.

Finally, I wish to speak of the part played by Dr. Owens as one of the early members of the American Surgical Association. It is just thirty-two years ago since a few men conceived the idea of organizing an association which should be unequaled as regards the professional standing of its members. The organization was started with a comparatively small body of men, whose idea was to limit the membership to those who were not only great surgeons from the standpoint of the patient, but who were also identified with the progress and betterment of surgery. The American Surgical Association has been elastic enough to take in all the highest types of men and no others. It can be compared to no other association of its kind in the world, and may well be said to be a monument to its founders. Dr. Owens has been one of the guiding spirits of this great association since its foundation.

In view of the part Dr. Owens has played in the development of surgical work in America; in view of his great work in elevating the standards of his profession and developing means for alleviating human suffering, we can well afford to offer our congratulations, our esteem, and admiration for the dignity and retiring perseverance of the man who has so steadily and surely accomplished his work.

LAYING OF THE CORNER-STONE

On October 10, 1912, the corner-stone was laid for the new office, laboratory , and library building in process of erection for the Mayo Clinic. This building occupies the northwest quarter of the block, in which are situated at present the offices of the Mayo Clinic, and on land purchased by Dr. W. W. Mayo in 1863 and 1864. In the center of the corner-stone was placed a copper box containing various statistical information, photographs, coins, etc.

Dr. William J. Mayo defined the purpose of the structure in brief as follows: "The object of this building is to furnish a permanent house wherein scientific investigation can be made into the cause of the diseases which afflict mankind, and wherein every effort shall be made to cure the sick and the suffering. It is the hope of the founders of this building that in its use the high ideals of the medical profession will always be maintained. Within its walls all classes of people, the poor as well as the rich, without regard to color or creed, shall be cared for without discrimination."

INDEX OF CONTRIBUTORS

PAGE

Alexander Archibald and H. Z. Giffin:
  Sacrococcygeal Sinus (Postanal Dermoid) 658
Donald C. Balfour:
  Drainage of Wounds 748
  The Occurrence of Right Inguinal Hernia Following Appendectomy.... 242
  An Operating-room Mirror 693
E. H. Beckman:
  Complications Following Surgical Operations 738
  The Open Treatment of Fractures 673
  The Repair of Hernia from the Peritoneal Side of the Abdominal Wall.. 240
  An Unusual Bone Tumor of the Foot 678
John Minor Blackford and William Carpenter MacCarty:
  Involvement of Regional Lymphatic Glands in Carcinoma of the Stomach 90
William F. Braasch:
  Clinical Data on Malignant Renal Tumors 289
  The Clinical Diagnosis of Congenital Anomalies in the Kidney and Ureter 249
  A Neglected Principle in Cystoscopy 338
  The Results of the Early Diagnosis of Urinary Tuberculosis 280
William F. Braasch and John William Draper:
  The Function of the Ureterovesical Valve 324
John William Draper and William F. Braasch:
  The Function of the Ureterovesical Valve 324
George B. Eusterman:
  Notes on the Dyspepsias. With Special Reference to Diagnosis 8
H. Z. Giffin:
  Clinical Observations Concerning 27 Cases of Splenectomy 449
  The Diagnosis of Diaphragmatic Hernia 225
  The Diagnosis of Diseases Associated with Enlargement of the Spleen.. 441
  The Diagnosis of Diverticulitis of the Large Bowel 148
H. Z. Giffin and Alexander Archibald:
  Sacrococcygeal Sinus (Postanal Dermoid) 658
Gertrude Booker Granger:
  Analysis of 13,000 Cases for Errors of Refraction 629
M. S. Henderson:
  Regeneration of the Tendons 665
Edward Starr Judd:
  Cesarean Section and Cesarean-Porro Operation 422
  The Functional Results in Prostatectomy 368

PAGE
Prostatectomy.................... 376
Results in the Treatment of Tumors of the Urinary Bladder.......... 343
Tumors of the Urinary Bladder.................... 353
William Carpenter MacCarty:
Goiter and Its Relation to Its Structural and Physiologic Units....... 546
Pathologic Anatomy of Goiter (a Macroscopic and Microscopic Study of Fresh Material from 2500 Cases).................... 536
William Carpenter MacCarty and John Minor Blackford:
Involvement of Regional Lymphatic Glands in Carcinoma of the Stomach 90
William Carpenter MacCarty and Walter E. Sistrunk:
Benign and Malignant Ovarian Cysts.................... 393
Justus Matthews:
The Relation of Nasal Conditions to Anaphylaxis and Asthma........ 635
Charles H. Mayo:
Diverticula of the Gastro-intestinal Tract: Their Surgical Importance 188
Factors of Safety in Operating for Exophthalmic Goiter.............. 508
Goiter.................... 513
Observations on German Surgery.................... 791
The Surgery of the Single and Horseshoe Kidney.................... 265
Charles H. Mayo and Bernard Francis McGrath:
The Surgical Importance of the Thymus: A Review of the Question... 556
William J. Mayo:
Address, February 10, 1912.................... 800
Contributions of the Nineteenth Century to a Living Pathology........ 711
Grafting and Traumatic Dissemination of Carcinoma in the Course of Operations for Malignant Disease.................... 705
Jejunostomy.................... 129
Management of the Opening in the Transverse Mesocolon in Completing the Operation for Posterior Gastrojejunostomy.................... 683
Nephrectomy without Drainage for Tuberculous Kidney.............. 686
Operative Results in Carcinoma of the Gastro-intestinal Tract........ 135
The Radical Operation for the Relief of Cancer of the Rectum and Rectosigmoid.................... 203
A Short Visit to Some of the Hospitals in Germany, Austria, Switzerland, and Holland.................... 780
Some of the Disputed Problems Associated with Surgery of the Large Intestine.................... 142
Surgery of the Spleen.................... 469
Surgical Treatment of Prolapse of the Uterus and Walls of the Vagina... 429
Bernard Francis McGrath:
Intestinal Diverticula: Their Etiology and Pathogenesis.............. 156
Bernard Francis McGrath and Charles H. Mayo:
The Surgical Importance of the Thymus: A Review of the Question... 556
Henry S. Plummer:
Diffuse Dilatation of the Esophagus without Anatomic Stenosis (Cardiospasm).................... 3

A. H. SANFORD: PAGE
Malaria in Northern States.......... 763
Noguchi and Other Reactions.......... 752
WALTER E. SISTRUNK AND WILLIAM CARPENTER MACCARTY:
Benign and Malignant Ovarian Cysts.......... 393
FRANK SMITHIES:
The Diagnostic Significance of the Paravertebral Triangle of Percussion Dulness (Grocco's Sign).......... 640
The Diagnostic Worth of the Glycyltryptophan and the Tryptophan Tests in Diseases of the Stomach.......... 18
Gastric Ulcer without Food Retention.......... 66
The Glycyltryptophan (Peptid) Splitting Agent in Human Saliva...... 33
A Method for the Microscopic Examination of Gastric Extracts and of Feces.......... 699
Note on a Peptid-Splitting Agent in Human Blood-serum.......... 768
The Occurrence of Trichomonas Hominis in Gastric Contents, with a Report of Two Cases.......... 51
A Simplified Technic for the Application of the Glycyltryptophan Test to Gastric Contents.......... 696
LEDA J. STACY:
Notes on Carcinoma of the Uterus.......... 415
G. T. THOMAS:
An Apparatus for the Injection and Lavage of the Pelves of the Kidneys and the Ureters.......... 689
LOUIS BLANCHARD WILSON:
The Embryogenetic Relationships of Tumors of the Kidney, Suprarenal and Testicle.......... 303
Fatal Postoperative Embolism.......... 727
Graduate Instruction in Medicine.......... 770
The Microscopic Examination of Fresh Tissues for the Diagnosis of Early Cancer.......... 721
The Pathology of Splenomegaly: A Study of the Operative and Autopsy Material from the Mayo Clinic.......... 482
The Relationship of the Clinical and Pathologic Aspects of Exophthalmic Goiter.......... 525

BIBLIOGRAPHIC INDEX

Abbott, 329
Abderhalden, 18, 32, 768, 769
Abelin, 579, 622
Abt, 768, 769
Adami, 470, 481, 507, 622
Albarran, 324, 337
Albert, 475, 481, 491, 506
Alexander, 372, 431, 432, 438
Alexieff, 63, 65
Ambrosini, 622
Anders, 264
Anderson, 637, 639
Andrews (Edmund), 801
Archibald, 658, 764
Armstrong, 472, 481
Aroaz, 642, 657
Ashhurst, 160, 187
Auer, 637, 639
Autertin, 622

Bachrach, 785
Baduel, 642, 643, 648, 656
Balfour, 202, 222, 242, 693, 748
Bang, 563, 622
Banti, 472, 481, 502, 506, 642, 656
Barbano, 562, 566, 607, 623
Barbieri, 642, 657
Bartel, 560, 594, 595, 596, 597, 598, 599, 600, 601, 602, 610, 611, 612, 613, 622, 623, 661
Bartlett, 676
Basch, 561, 566, 569, 571, 573, 615, 623, 625
Baumann, 543, 545, 547, 555
Bayer, 610, 623
Beall, 642, 643, 657
Becker, 225, 234, 239, 557, 623
Beckman, 236, 239, 240, 673, 678, 738
Bednar, 575, 623
Beer, 187
Belfield, 339
Beltz, 225, 239
Beneke, 591, 623
Beresnegowsky, 337
Bergmann, 783
Bernheim-Karrer, 595, 623
Bevan, 209, 222
Bianchi, 623
Bianthi, 615
Bier, 782, 783, 788, 792
Bigelow, 57, 61
Billings, 134
Billroth, 99, 104, 797
Birch-Hirschfeld, 589, 623
Bircher, 542, 544, 546, 555, 609, 610, 623
Birnbaum, 604, 623
Bischoff, 574, 623
Bittorf, 156, 187, 602, 623
Blackford, 90
Blake, 674, 677
Bland-Sutton, 173, 187
Bloodgood, 191, 201, 202
Blum, 285, 288, 543, 545, 547, 555
Blumenreich, 615, 623
Blumer, 642, 657
Bockenheimer, 273, 279
Boehm, 692
Bond, 142, 147
Bonnet, 574, 623
Bordate, 618
Bordet, 752, 622
Born, 560, 623
Borst, 665, 672
Bourneville, 572, 574, 623
Bovaird, 497, 506, 566, 623

Boyd, 378, 392
Bozzolo, 99, 104
Braasch, 249, 264, 276, 279, 280, 288, 289, 294, 324, 325, 338, 341
Branco, 321, 323
Bresseta, 321, 323
Brewer, 187
Brill, 445, 498, 506, 507
Bruck, 752
Brudzinski, 642, 657
Bryant (Thomas), 800
Bucco, 642, 656
Bumm, 792, 794
Bunts, 798
Bush, 444, 448
Byrnes, 708

Cabot, 443, 448, 507, 640, 656
Calvert, 642, 646, 657
Canfield, 58
Cannon, 85, 142, 147, 718
Capelle, 604, 605, 610, 617, 623
Capobianco, 566, 623
Carlier, 272, 279
Carpenter, 575, 623
Carrel, 719
Carstens, 480, 481
Cassaet, 642, 657
Cathelin, 324, 335, 337
Cecchini, 642, 656
Chassaignac, 748
Chatin, 543, 545, 547, 555
Chiari, 576, 623
Chlumsky, 171, 187
Christofoletti, 786
Clairmont, 134, 785, 797
Clark, 498, 574, 623
Clegg, 51, 64
Clessin, 591, 623
Clogg, 193, 202
Coffey, 147, 333
Cohn, 727
Cohnheim, 52, 63, 64, 727
Coley, 183
Collier, 497, 506
Collin, 566, 623
Cornil, 415
Craig, 754, 762
Crenshaw, 374
Crile, 436, 438, 512, 547, 710, 719
Cripps, 141, 198, 202, 209, 222
Cruveilhier, 158, 187
Cullen, 415, 416, 421
Cumming, 65, 768, 769
Cuneo, 91, 95, 96, 97, 99, 104
Cunningham, 63, 65, 266
Cushing, 718
Czerny, 601, 623

Da Costa, 640, 656
Dare, 68
Darwin, 713
Daut, 536, 592
Davaine, 63, 65
Davis, 423, 425, 426, 427, 428, 665, 672, 708
Deaver, 423, 428
de Barros, 642, 657
Decker, 337
de Jong, 499, 507
Derselbe, 623
Dieffenbach, 783
Disse, 328
Dock, 51, 52, 60, 63, 64, 65, 506, 656
D'Oelsnitz, 615, 616, 623
Donne, 52, 63, 64, 65
Dorner, 448
Downey, 490, 507
Draper, 324
Dreschfeld, 604, 623
Drobnik, 665, 672
Dubois, 576, 623
Dudgeon, 563, 567, 623
Dufour, 642, 657
Durham, 660
Dwornitschenko, 606, 623

Eastman, 436, 438
Elberle, 576, 623
Edel, 171, 187
Ehrlich, 563, 623, 797

Eiselsberg, 542, 545, 546, 555, 784, 785, 797
Elsner, 339
Emerson, 32
Emery, 760, 762
Enderlen, 796
Epstein, 63, 65
Erickson (John), 800
Escherich, 595, 596, 623
Eternod, 659
Eusterman, 8, 765
Ewart, 642, 643, 648, 650, 653, 655, 657
Ewing, 318, 319, 321, 322, 323

FABYAN, 642, 650, 652, 653, 657
Fagge, 204, 222
Fajerstajn, 604, 623
Falconer, 193, 202
Farret, 581, 623
Feer, 586, 623
Felix, 319, 323
Fenger (Christian), 801
Fenwick, 15, 17
Ferguson, 354
Ferrannini, 642, 651, 656, 657
Fielder, 160, 187
Finney, 143, 147
Fischer, 18, 19, 20, 32, 34, 575, 624, 696, 768, 769
Fitz, 715, 716
Fleiner, 3, 7
Flexner, 760
Flora, 642, 656
Forbes-Ross, 642, 648, 657
Förster, 271, 279
Fortescue-Brickdale, 568, 574, 623
Fowler, 475, 481
Franke, 444, 448, 474, 481
Frankenheimer, 642, 653, 657
Frankenthal, 434, 438
Franz, 783, 792, 793
Freund, 51, 60, 62, 64, 271, 279
Freyer, 371
Friedjung, 596, 624
Friedländer, 618, 623
Friedleben, 559, 560, 567, 568, 574, 579, 623
Fürth, 575, 623

GAGSTATTER, 337
Ganghofner, 596, 624
Garré, 605, 624, 788, 796
Gaskell, 514
Gaucher, 467, 475, 481, 497, 498, 506
Gebele, 605, 609, 624
Gebhardt, 268, 279
Geraghty, 378, 392
Gerard, 272, 279
Gerota, 104
Gerster, 275, 279
Ghelfi, 642, 657
Gibbon, 273, 279
Gierke, 605, 609, 624
Gies, 27, 32, 33
Giffin, 148, 155, 187, 225, 239, 441, 449, 482, 506, 658, 764
Gluck, 606, 624
Glynn, 309, 312, 313, 315, 323
Goldflam, 603, 624
Goldscheider, 642, 657
Goldzieher, 600
Good, 171
Goodel, 77
Gordinier, 158, 187, 642, 643, 653, 657
Graham, 764, 765
Grandhomme, 624
Granger, 629, 764
Graser, 157, 158, 171, 187
Grassi, 63, 65
Graves, 148, 155
Grawitz, 308, 318, 323, 591, 624
Griffith, 624
Grocco, 640, 641, 642, 643, 652, 653, 654, 655, 656, 657
Grocz, 622, 626
Groschuff, 560
Grosser, 529
Grosz, 594, 598, 601
Gunn (Moses), 800
Gurd, 759, 762
Guret, 353

Haberda, 591
Hall, 19, 32
Halle, 595
Halstead, 547
Hammar, 558, 559, 560, 562, 563, 564, 565, 566, 573, 576, 594, 596, 609, 612, 613, 620, 622, 624
Hanau, 171, 187
Handley, 204, 222
Hansemann, 66, 77, 158, 171, 187, 609, 624
Harris, 437, 438, 497, 506
Hasse, 579, 624
Hart, 558, 560, 565, 566, 574, 579, 580, 591, 592, 594, 597, 598, 599, 600, 609, 610, 613, 619, 624
Hartmann, 220, 222
Haudick, 792
Hedinger, 591, 595, 596, 598, 600, 601, 602, 605, 610, 624
Heer, 603
Heidenhain, 624, 709
Heineke, 563, 567, 624
Henderson, 665
Henle, 566, 624
Hennig, 624
Herczel, 499, 507
Herrmann, 612
Hertzig, 566
Herz, 604, 624
Herzog, 497, 506
Heschl, 171
Heuer, 272, 279
Hildebrand, 792, 795
Hill, 437, 438
Hinrichs, 624
His, 91, 104, 566, 624
Hochenegg, 187, 212, 222, 785, 797
Hodenpyl, 158, 187
Hofmeister, 793
Hoguet, 242, 245
Holmes (Oliver Wendell), 800
Honan, 778
Honnicke, 610
Hönnike, 624
Hornowski, 572, 624
Horsley, 542, 544, 546, 555, 718
Hotz, 579, 619, 624
Howell, 328
Howland, 567, 624
Hunt, 63, 65
Hunter (John), 711, 712, 713, 717
Huntington, 267, 304, 323, 335, 337

Ingalls, 234, 239
Israel, 285, 288

Jackson, 144, 147, 624
Jackson (Chevalier), 619
Jacobi, 624
Jaksch, 63, 65
Jamburger, 642, 657
Jedlicka, 784
Jelle, 309, 323
Jenner, 711
Jepson, 475, 481, 491, 506
Jeriselum, 785
Jermain, 766
Joffray, 604, 624
Johnson, 480, 481, 564, 624, 766
Jonnesco, 203, 222, 474, 481
Judd, 343, 353, 368, 376, 422

Kaiserling, 566, 624
Kaplan, 579, 581, 583, 589, 624
Kassowitz, 591, 596, 624
Keibel, 266, 323, 529
Keith, 189, 191, 194, 202
Kelly, 278, 325, 338, 339, 342
Kemp, 187
Kendall, 187
Kivlin, 158, 187
Klebs, 171, 187
Klose, 568, 569, 571, 572, 573, 580, 618, 619, 624, 626
Kober, 19, 32
Koch, 339, 624
Kocher, 435, 436, 438, 508, 547, 605, 624, 787
Kohlenberger, 19, 32

Kolisko, 594, 597, 599, 624
Kölliker, 560, 566, 624
Kollmann, 561, 659
König, 273, 279, 589, 624
Königer, 225, 226, 239
Kopp, 624
Korànyi, 641, 642, 652, 656
Körte, 783, 792, 797
Kostlivy, 557, 624
Kraske, 141, 210, 220, 222
Krause, 3, 792
Kromayer, 564
Krompecher, 499, 507
Kropeit, 325, 337
Kukula, 784
Kümmell, 781, 782, 793, 798
Küster, 268, 279, 353, 424, 428
Kutscher, 624
Kyrle, 612, 624

LAKIN, 202
Lamieris, 789
Landa, 642, 643, 655, 657
Lane, 146, 147, 673, 676
Lang, 625
Lange, 591, 665, 672
Langenbeck, 783
Lanz, 788, 789
Laqueur, 603, 625
Larrier, 563
Lasvenes, 604, 624
Laurell, 563
Lazarus, 563
Le Conte, 234, 239
Lejars, 625
Lengemann, 91, 97, 98, 104
Lenhart, 604, 625
Lenhartz, 63, 65
Lenormant, 606, 624
Letulle, 563, 577, 625
Leubuscher, 591
Leuckhart, 63, 64
Lewis, 268, 279, 325, 338, 339, 342, 507, 637, 639, 665, 672
Lexer, 795, 796
Leyden, 52, 63, 64, 65
Libman, 497, 498, 507
Lilienthal, 206, 218, 222
Lister, 714
Litten, 63, 64
Lorand, 515
Lossen, 7
Lower, 479
Lowsley, 377, 392
Lucas, 337
Lucien, 566, 623, 625
Luys, 339, 342
Lyle, 19, 32, 142, 147
Lyon, 502, 507

MACCARTY, 25, 32, 90, 91, 92, 104, 200, 202, 393, 405, 514, 543, 545, 546, 547, 555, 667, 726
Mackenrodt, 434, 438
Magneson, 676
Makkas, 796
Mall, 323, 529
Mallory, 660
Mandelbaum, 497, 498, 499, 507
Maragliano, 642, 656
Marchand, 497, 498, 499, 502, 506
Marfan, 595, 625
Marine, 535, 538, 544, 552, 604, 625
Markoe, 423, 425, 426, 428
Martin, 3, 7, 430, 438, 676
Matas, 719
Matthews, 635
Matti, 560, 561, 569, 570, 571, 573, 605, 625
Maximow, 562, 625
May, 63, 65
Maydl, 333, 784
Mayer, 569, 625
Mayo (Charles H.), 66, 163, 188, 208, 265, 508, 509, 513, 535, 547, 556, 588, 791
Mayo (William J.), 11, 66, 129, 135, 142, 143, 147, 155, 158, 163, 171, 187, 203, 208, 222, 261, 277, 279, 325, 429, 441, 466, 468, 469, 482, 509, 683, 686, 705, 711, 749, 751, 780, 800, 803
Mayo (W. W.), 803

Mayo-Robson, 134, 193
McBurney, 334
McCardie, 625
McConnell, 475, 481
McGlumphy, 65
McGrath, 148, 155, 156, 200, 202, 556, 726
McGuire, 615, 625
Melchior, 606, 625
Meltzer, 3, 7, 637, 639, 719
Mensi, 563, 625
Mettenheimer, 581, 607, 625, 626
Meyer, 618, 625
Mietens, 566, 625
Mikulicz, 3, 7, 91, 196, 197, 198, 201
Miles, 220, 222
Millet, 339
Mixter, 190, 717
Moebius, 517, 625
Mölders, 596, 625
Monro, 264
Morison, 642, 657
Most, 95, 104
Mraček, 575
Muller, 18, 32
Mullin, 755
Murphy, 795
Musgrave, 51, 64
Musser, 445, 448
Myers, 618, 625

Nathan, 563, 625
Neisser, 752
Neubauer, 18, 19, 20, 32, 34, 696, 768, 769
Neufville, 271, 274, 279
Neumann, 625
Neusser, 560, 594, 596, 597, 598, 600, 601, 602, 616, 622, 625
Newell, 424, 428
Nicoll, 566, 623
Nicolle, 768, 769
Nicolodoni, 665, 672
Nitze, 338, 342
Noble, 438
Noguchi, 752, 753, 754, 755, 757, 760, 761
Nordmann, 573, 625
Nothnagel, 763
Notkin, 543, 545, 547, 555

Ochsner, 240
Ogden, 766
Oidtmann, 543, 545, 547, 555
Oliver, 569
Olivier, 618, 625
O'Malley, 498, 507
Oppenheim, 19, 32, 625
Oppenheimer, 603, 604
Orgler, 566, 625
Orth, 99, 104
Oser, 625
Osler, 443, 448, 455, 472, 481, 487, 502, 506, 507, 763
Oswald, 538, 543, 544, 547, 555
Otto, 637, 639
Owens (John E.), 800, 801, 802

Padoa, 642, 656
Paltauf, 594, 596, 625
Pappa, 324, 337
Pappenheimer, 563, 564, 600, 610, 613, 614, 625
Pares, 557, 626
Parisot, 625
Park, 615, 625
Parkes (Charles T.), 801
Pasteau, 337
Pasteur, 713, 714
Pawlick, 784
Pawlow, 718
Payr, 542, 545, 546, 555, 794, 795
Péan, 436
Peck, 210, 222
Pedrazzini, 619
Pennato, 642, 656
Perthes, 787, 788, 794, 795, 796
Petit, 226
Petren, 605, 625
Petrick, 99, 104
Pettenkofer, 30
Pfaundler, 601, 624, 625

Pichad, 784
Picou, 497, 506
Picqué, 337
Pierracini, 642, 656
Piersol, 328, 337
Pietkerwicz, 337
Pilcher, 370, 380, 438, 751
Plater, 559, 625
Plehn, 499, 507
Plessi, 652, 657
Plummer, 3, 7, 190, 202, 509, 517, 525, 526, 527, 528, 534, 535
Pond, 242, 245
Popoff, 321, 223
Popper, 573, 625
Porro, 422, 427, 428
Pottenger, 640, 656
Powers, 475, 481
Prenant, 560, 562, 564, 625
Price, 436
Pröbsting, 589, 625
Prowazek, 63, 65
Pruneda, 642, 657
Purrucker, 587, 625

Quénu, 141, 209, 222

Rabe, 560, 625
Ram, 368
Ramond, 497, 506
Ranconi, 626
Rauchfuss, 641, 642, 646, 652, 656, 657
Recklinghausen, 596, 601, 626, 732
Rehn, 518, 596, 605, 610, 626, 791, 797
Reilly, 642, 657
Rendu, 604, 625
Renner, 91, 97, 98, 104
Rettig, 499, 507
Reverdin, 542, 544
Rhein, 225, 239
Richardson, 665, 672
Richter, 596, 625
Riddle, 566
Riedel, 605
Rindfleisch, 99, 104
Risel, 499, 507
Ritchie, 563, 626
Robin, 415
Robinson, 268, 270, 271
Robson, 134, 193
Roch, 642, 657
Rohn, 566, 615, 623, 625
Rokitansky, 143, 147, 189, 202, 625, 705
Rolleston, 497, 506, 566, 589, 625
Ronconi, 564, 566
Röntgen, 719
Roos, 543, 545, 547, 555
Rosenau, 637, 639
Rosenberg, 625
Rosenbloom, 19, 27, 32
Rosenfeld, 52, 64
Rosenheim, 3, 7
Ross, 699
Rössle, 600, 604, 609, 626
Rotgans, 788, 789
Rovsing, 147, 251, 264, 273, 279
Rubaschow, 625
Rudberg, 563, 564, 567, 617, 626
Ruhräh, 566, 625
Russel, 5, 7
Rydygier, 665

Sahli, 607, 626
Sailer, 225, 239
Sampson, 158, 187, 421
Sanford, 19, 27, 32, 752, 763
Sänger, 424, 425, 427, 428
Sappey, 95, 104, 568, 626
Sauerbruch, 719
Scagliosi, 607
Schäffer, 563, 564, 569, 626
Schauta, 786, 794
Schede, 783, 788
Scheele, 626
Schewkunenko, 337
Schiff, 542, 544, 546, 555
Schlagenhaufer, 498
Schlesinger, 576, 626
Schloffer, 783
Schlossman, 624

Schmidt, 337, 596, 626
Schmidt (M. B.), 569
Schräder, 415, 421
Schraube, 626
Schreiber, 171
Schridde, 616, 622, 626
Schultz, 572, 626
Schwinn, 617, 626
Seggle, 665, 672
Seiler, 572, 626
Selby, 236, 237
Serrelach, 557, 626
Sever, 665, 672
Shaw, 448
Shiota, 600, 626
Siciliano, 642, 643, 648, 656
Sick, 781, 782
Sievers, 3, 7
Signorelli, 642, 657
Silvestri, 642, 656
Simonds, 502, 507
Sippy, 5, 7, 502, 506
Sisson, 309, 323
Sistrunk, 51, 53, 64, 393
Skaller, 51, 64
Smith, 626, 642, 646, 657
Smith (A.), 615
Smith (Theobald), 637
Smithies, 18, 20, 33, 34, 51, 66, 640, 642, 657, 696, 699, 768
Snell, 339
Sokoloff, 566, 571, 626
Springthorp, 498, 506
Squier, 388, 392
Ssokolow, 509, 606, 626
Stacy, 415, 764
Starling, 718
Steffen, 575
Stein, 594, 610, 611
Stengel, 497, 498, 506
Sternberg, 444, 448
Stirling, 498, 506
Stitt, 760
Stoerck, 309, 323
Stöhr, 562, 563, 626
Stoltz, 430, 438
Strauss, 66, 77
Strube, 52, 64
Strümpell, 602, 626
Strüppler, 225, 226, 239
Sudeck, 309, 323
Sudsuki, 158, 171, 187
Sullivan, 333
Sury, 566, 574, 587, 591, 592, 595, 596, 600, 626
Svehla, 569, 610, 626
Syk, 563, 626

Tait, 333, 436, 437, 438, 715
Tandler, 377, 392, 560, 594, 598, 601, 622, 626
Taylor, 202, 767
Telling, 159, 160, 171, 173, 179, 184, 185, 187, 192, 202
Testut, 568, 626
Tharling, 605, 625
Thayer, 642, 650, 652, 653, 657
Theobald, 63, 65
Thomas (G. J.), 689
Thompson, 193, 202, 269, 279, 325, 337, 778
Thorbecke, 604, 617, 626
Tillmanns, 275, 279, 605, 797
Töpfer, 77
Trendelenburg, 210, 212, 787, 788, 797
Treves, 158, 187, 203, 222
Trotter, 309, 323
Türk, 444, 448
Tuttle, 141, 204, 209, 222

Uffelmann, 29
Umber, 498, 506

Van Arsdale, 750
Van Heukelom, 499, 507
Van Lier, 617, 625
Vaughan, 64, 65, 768, 769
Vellemin, 596
Vincent, 566, 569, 626
Virchow, 156, 157, 187, 195, 202, 323, 578, 579, 596, 601, 626, 705, 713, 727

Vogt, 571, 572, 573, 580, 619, 624, 626
von Bergmann, 783
von Eiselsberg, 542, 545, 546, 555, 784, 785, 797
von Hansemann, 609
von Herczel, 499, 507
von Jaksch, 63, 65
von Korànyi, 641, 642, 652, 656
von Leyden, 52, 63, 64, 65
von Mettenheimer, 581, 625
von Neusser, 560, 594, 596, 597, 598, 600, 601, 602, 616, 622, 625
von Recklinghausen, 596, 601, 626, 732
von Strümpell, 602, 626
von Sury, 566, 574, 587, 591, 592, 595, 596, 600, 626
von Wiesner, 610, 612
Vulpius, 665, 672

WAGNER, 415, 421
Wainwright, 416, 421
Waldeyer, 328, 415, 565, 626
Walker, 51, 64, 194, 202
Wallis, 220, 222
Warfield, 19, 27, 32, 33, 37, 50
Warthin, 53, 473, 481, 502, 506
Wassermann, 14, 752
Watkins, 433, 434, 435, 438
Weber, 448
Weichselbaum, 467, 475, 497, 506, 626
Weidenreich, 490, 507, 562, 626
Weigert, 603, 626
Weil, 618, 626, 641, 656, 760, 761, 762
Weinstein, 19, 20, 27, 28, 32, 33, 50, 698
Weinstrand, 569
Weisflog, 576, 626
Weitz, 642, 657
Welch, 416, 421, 727, 748, 751
Wentworth, 502, 506
Wertheim, 208, 433, 434, 435, 438, 785, 786, 794
Wharton, 567, 626
White, 368
Whitney, 717
Wiesel, 559, 560, 568, 573, 574, 575, 576, 579, 586, 589, 592, 594, 596, 597, 598, 600, 601, 602, 603, 605, 609, 610, 612, 613, 614, 618, 622, 625, 626
Wiesner, 610, 612, 626
Wildbolz, 285, 288
Wildner, 491, 506
Williamson, 19, 32, 497, 506
Willis, 726
Willy, 58
Wilms, 144, 147, 306, 307, 321, 323, 795, 796, 798
Wilson, 155, 171, 179, 184, 187, 199, 202, 268, 279, 303, 323, 441, 461, 468, 482, 525, 535, 721, 726, 727
Wilson (Louis B.), 770
Windscheid, 155, 187
Witter, 54
Witzel, 129
Wölfler, 511, 783
Wright, 768, 769
Wulff, 325

YOUNG, 331, 332, 337

ZABEL, 52, 64
Zehbe, 309, 323
Zender, 99, 104
Zenker, 3, 7
Zesos, 605, 626
Ziegler, 323
Ziemssen, 7
Zuckerkandl, 377, 392, 785, 797

INDEX OF SUBJECTS

Abbott's method for cutting ureters in dogs, 329
Abdominal extraperitoneal cesarean section, 424
  wall, repair of hernia from peritoneal side of, 240
Abscess as cause of splenic enlargement, 445
  Dubois', in syphilis of thymus, 576
  of thymus, 574, 575
Accidental thymic involution, 567
Acid, butyric, test, in diagnosis of syphilis, 761
  organic, relation of glycyltryptophan test to, 29
    relation of tryptophan test to, 29
Acidity in ulcer of stomach without food retention, 77–83, 88
  relation of glycyltryptophan test to, 27
    of tryptophan test to, 28
Addison's disease, status thymicolymphaticus and, relationship, 602
Adenoma of thyroid, 531
Adenomatosis of thyroid, 531
Adhesions in large intestine, 144
Adolescence, goiter of, 517
    iodin in, 517
Adrenal gland, tumors of, embryogenetic relationships of, 303, 313, 322
Adrenals in status thymicolymphaticus, 600
Alexander exercises after prostatectomy, 372
Alimentary canal, 1
Alphozone solutions, action of, on peptid-splitting power of saliva, 44, 45
Amboceptor, 752
Amebæ in gastric contents, 51
Amsterdam, surgical work at, 788
Amyloid degeneration in thyroid, 533
Anaphylaxis, relation of nasal conditions to, 635
Anatomy of thymus, 564
    topographic, 579
Anemia, pernicious, associated with dyspepsia, 15
    enlargement of spleen in, 445
    splenomegaly in, 467
  splenic, 446, 449, 450, 472
    blood-findings in, 455–457, 472
    cirrhosis of liver in, 459
    contour and position of spleen in, 451–454
    diarrhea in, 458
    enlargement of spleen in, 451
    fever in, 458
    hematemesis in, 455
    jaundice in, 459
    leukocyte count in, 455
    malaria in, 459
    pain in, 458
    pathology of, 487
Anesthesia, ether, in operations for exophthalmic goiter, 512
    for goiter, 518
Antibody, syphilitic, 755
Antigen, syphilitic, 754
Aorta, narrowness of, in status thymicolymphaticus, 600
Apparatus for injection and lavage of pelves of kidneys and ureters, 689
Appendectomy, occurrence of right inguinal hernia after, 242
Appendiceal dyspepsia, 13
Appendix, vermiform, alterations in, in ulcer of stomach without food retention, 84
    diverticula of, 194

Asthma, relation of nasal conditions to, 635
  thymic, 578
Atrophic kidney, 256
Atrophy of thyroid gland, 532
  of ureter, 257
Austria, hospitals of, visit to, 780

BACTERIA, effect of, on cleavage of glycyltryptophan, 46, 48
Berlin, surgical work at, 782
Bern, surgical work at, 787
Bile, relation of, to glycyltryptophan test, 30
    to tryptophan test, 30
Bladder, cancer of, 355
  examination in diverticulitis of large intestine, 152
  fibromyoma of, 355
  papilloma of, 343, 355
  tumors of, 353
    anatomic findings, 354
    cystoscopic examination in, 345
    diagnosis, 360
    electricity in, 351, 365
    etiology, 354
    frequency, 353
    fulguration in, 351, 365
      results, 367
    hematuria in, 356
    involvement of prostate in, 346
    pain in, 358
    prognosis, 361
    surgical treatment, methods of, 344
        results of, 343, 346
    symptoms, 356
    treatment, 363
Blake's operation for fracture of patella, 677
Blastema, renal, 266
Blood count in diverticulitis of large intestine, 152
  formation, influence of thymectomy on, 572
  in gastric extracts, relation of, to glycyltryptophan test, 30, 31
        to tryptophan test, 30, 31
Blood in stools in diverticulitis of large intestine, 152
Blood-clot, formation of, influence of thymic extract in, 573
Blood-corpuscles, red, in thymus, 564
Blood-findings in enlargement of thymus, 616, 617
  in splenic anemia, 455–457, 472
Bloodgood's operation for diverticula of large intestine, 201
Blood-serum, human, peptid-splitting agent in, 768
Bone tumor of foot, 678
Bones, sesamoid, in sole of foot, 680
Bonn, surgical work at, 788
Braasch's cystoscope, 341
Bright's disease associated with dyspepsia, 14
Bronchitis, postoperative, 741, 743
Bronchocele, 188
Bronchopneumonia, postoperative, 742, 743
Butyric acid test in diagnosis of syphilis, 761

CALCAREOUS degeneration in thyroid, 533
Canal, alimentary, 1
Cancer, chronic irritation as factor in cause of, 716, 722
  diagnosis of, early, microscopic examination of fresh tissues for, 721
  frequency of, 415
  grafted on diverticulitis of large intestine, 200
  grafting of, 705
  mortality from, 415
  of bladder, 355
  of cervix uteri, frequency, 416
      symptoms, 417
  of gastro-intestinal tract, operative results in, 135
  of kidney, 289
  of large intestine, operative results in, 135
  of rectosigmoid, operability, 206

Cancer of rectosigmoid, radical operation for, 203
    first stage, 218
    second stage, 218
  of rectum, abdominal operation in, one stage, 212
    abdominoperineal operation in one stage, 212
    Cripps' perineal resection for, 209
    Hochenegg's operation for, 212
    Kraske's operation for, 210
    operability, 206
    operations for, local, 208
      through perineum or posterior sacral incision in single stage, 208
    operative results in, 140
    preliminary colostomy with secondary posterior resection, 217
    Quénu-Tuttle perineal resection for, 209
    radical operation for, 203
      colostomy in, 206
      first stage, 218
      Lilienthal's method of colostomy in, 206
      principles in technic, 204
      second stage, 218
    tube operation, 214
  of small intestine, operative results in, 135
  of spleen, 445
  of stomach, accidental injuries to stomach during exploration, jejunostomy for, 133
    associated with dyspepsia, 13
    glycyltryptophan test in, 18, 19, 25
    involvement of regional lymphatic glands in, 90–128
    Neubauer and Fischer's test for, 19
    operative results in, 135
    tryptophan test in, 19, 25
    Weinstein's test in, 19
  of thymus, 577
  of uterus, 415
    age occurring, 419
    fibroids with, 420
Cancer of uterus, symptoms, 418, 419
  seeding of, 705
  traumatic dissemination of, 705
Capsule, renal, tumors of, embryogenetic relationships, 311
Cardiospasm, 3
Castor oil and balsam of Peru after removal of drain, 750
Cataract, congenital, 632
Catheter, ureteral, in malignant tumors of kidney, 296
Cecum, absorptive value, 142
Cells, eosinophilic, in thymus, 563
  lutein, in ovarian cysts, 394, 395
  of thymus, 561
  plasma, in thymus, 564
  reticulum, in thymus, 561
Cellulitis, postoperative, 745
Centrifugalization, effect of, on peptid-splitting power of saliva, 37
Cervix uteri, cancer of, frequency, 416
    symptoms, 417
Cesarean section, 422
    abdominal extraperitoneal, 424
    indications for, 422
    Sänger's method, 424, 425
    vaginal, 424
Cesarean-Porro operation, 422
Chemic solutions, effect of, on peptid-splitting power of saliva, 43–46
Chloroform, action of, on peptid-splitting power of saliva, 45
Cholecystitis in ulcer of stomach without food retention, 84
Cholelithiasis in ulcer of stomach without food retention, 84
Circulatory disturbances in malignant tumors of kidney, 292
Cirrhosis, Hanot's, splenic enlargement in, 446
  of liver in splenic anemia, 459
    primary, 466
    splenic enlargement in, 446
Cleavage of glycyltryptophan, effect of bacteria on, 46
Clot-formation, influence of thymic extract on, 573

Cobra-venom test of Weil for diagnosis of syphilis, 760
Coin-sound, 652
Colloid degeneration in thyroid, 533
Colon, diverticulum of, 195
Colostomy in radical operation for cancer of rectum, 205, 206
  Lilienthal's method, in cancer of rectum, 206
Complement for Noguchi reaction, 753
Congenital cataract, 632
Constipation in diverticulitis of large intestine, 151
Contributions of the nineteenth century to a living pathology, 711
Corner-stone, laying of, 803
Corpus luteum cysts, 393, 402
Cortex, renal, tumors of, embryogenetic relationships of, 305
Costocolic ligament, 136
Cough in malignant tumors of kidney, 295
Counter-test of Ewart, 650
Cripps' perineal resection for cancer of rectum, 209
Crucial test of Ewart, 650
Cystadenoma of ovary, 399, 405
Cystic spleen, diagnosis, 445
Cystoscope, Braasch, 341
  direct, 338
    advantages of, 340
    method of using, 341
Cystoscopic data in malignant tumors of kidney, 295
  examination in tumors of bladder, 345
  inspection in malignant tumors of kidney, 295
Cystoscopy, direct cystoscope, 339
  neglected principle in, 338
Cysts, corpus luteum, 393, 402
  dermoid, of ovary, 393
  hemorrhagic, of ovary, 393, 402
  of spleen, 475
  of thymus, 578
    in syphilis of thymus, 576
  of thyroglossal duct, 514
  ovarian, benign, 393
Cysts, ovarian, dermoid, 393
    hemorrhagic, 393, 402
    linings of, 394, 395
    lutein cells in, 394, 395
    malignant, 393
    simple, 397
    tarry, 401
  parovarian, 393
  tarry, of ovary, 401
Cytodiagnosis as aid in diagnosis of syphilis of nervous system, 762

DEATH, eczema, 595
  thymic, 559, 578
Degeneration, terminal, in thyroid gland, 533
Dermoid cysts of ovary, 393
  postanal, 658
    diagnosis of, 664
Diaphragm, elevation of, diaphragmatic hernia and, differentiation, 226
Diaphragmatic hernia, diagnosis, 225
    x-rays in, 228
    elevation of diaphragm and, differentiation, 226
    esophageal stenosis from, 236
    hydropneumothorax and, differentiation, 235
    pneumothorax and, differentiation, 234
    pyloric stenosis from, 236
    pyopneumothorax and, differentiation, 235
    subdiaphragmatic pyopneumothorax and, differentiation, 235
Diarrhea in diverticulitis of large intestine, 151
  in splenic anemia, 458
Digestion, parenteral, 768
Dilatation, diffuse, of esophagus, 3
    diagnosis, 5
    etiology, 3
    treatment, 5
  of stomach, acute, postoperative, 745
Diphtheria, thymic, 575
Diverticula, false, 188

Diverticula, false, of intestine, 162, 172
  Meckel's, 194
  of colon, 195
  of common and hepatic ducts of liver, 193
  of esophagus, 189
    Plummer's test for diagnosing, 190
  of gastro-intestinal tract, 188
    surgical importance, 188
  of ileum, 194
  of jejunum, 194
  of large intestine, 192, 194
    Bloodgood's operation for, 201
    cancer grafted on, 200
    clinical diagnosis, 183
    content, 159
    diagnosis, differential, 200
    etiology, 156, 171
    Mikulicz's operation for, 201
    openings, 159
    operation in, 201
    pathogenesis, 156, 173
    pathologic examination, 184
    shape, 158
    size, 158
    structure, 158
  of rectum, 196
  of sigmoid, 195
  of stomach, 191
  of vermiform appendix, 194
  pharyngo-esophageal, 189
  true, 188
Diverticulitis of large intestine, age, 150
    bladder examination in, 152
    blood count in, 152
      in stools in, 152
    constipation in, 151
    diagnosis, 148
      preoperative, 149
    diarrhea in, 151
    leukocytosis in, 152
    manual examination in, 152
    nutrition, 150
    occupation, 150
    pain in, 150
    rectal examination in, 152
    sex, 150
Diverticulitis of large intestine, temperature, 152
    vomiting in, 151
    weight, 150
Drainage of wounds, 748
    choice of drain, 750
    disadvantages, 748
    indications, 749
    length of time, 750
Dubois abscess in syphilis of thymus, 576
Ductless glands, 439
Dulness, percussion, paravertebral triangle of, auscultatory phenomena over, 652
    constancy, 652
    diagnostic significance, 640
    in double effusions, 653
    inability to demonstrate, 653
    method of determining, 648
    palpation in, 652
    physical characteristics, 649
    position in thorax, 652
    theories as to mode of production, 643
Duodenal ulcer associated with dyspepsia, 9
    diagnosis, 10
    glycyltryptophan test in, 26
    tryptophan test in, 26
    ulcer of stomach and, differentiation, 12
Duplicated renal pelvis, 260
  ureter, 261
    division of, 262
    partial, 262
Dyspepsia, 8
  appendiceal, 13
  Bright's disease associated with, 14
  cancer of stomach associated with, 13
  chronic, 8
  diagnosis, 8
  disease of gall-bladder associated with, 12
  duodenal ulcer associated with, 9
  functional, 15
  pernicious anemia associated with, 15

Dyspepsia, pulmonary tuberculosis associated with, 14
  syphilis of liver associated with, 14
    of stomach associated with, 14
  ulcer of stomach associated with, 12

Ectopic kidney, 258
Eczema death, 595
Electricity in tumors of bladder, 351, 365
Elevation of diaphragm, diaphragmatic hernia and, differentiation, 226
Embolism, postoperative, 727
    causes, 732
    prevention, 733, 736, 737
    pulmonary, 741
Embryology of thymus, 560
Embryoma of kidney, 289
Emery's modification of Noguchi reaction, 760
Endothelioma of spleen, Gaucher type, diagnosis, 445
Endothelium of spleen, primary proliferation of, 491
Enlargement of kidney and enlargement of spleen, differentiation, 442
  of spleen, abscess as cause, 445
    and enlargement of kidney, differentiation, 442
    and gall-bladder disease, etiologic relationship, 462
    conservative surgery in, 473
    diagnosis of diseases associated with, 441
      of various forms, 441
    in acute infections of childhood, 443
    in cirrhosis of liver, 446
    in Hanot's cirrhosis, 446
    in hemochromatosis, 446
    in Hodgkin's disease, 446
    in jaundice, 447
    in kala-azar, 447
    in leukemia, 445
    in malaria, 443
    in myelogenous leukemia, 471
Enlargement of spleen in pernicious anemia, 445, 467
    in polycythemia, 445
    in pseudoleukemia, 445
    in rickets, 443
    in splenic anemia, 451
    in tuberculosis, 443
    in typhoid fever, 443
    in Weil's disease, 447
    infarcts as cause, 445
    infections, 463
    pathology, 482
    surgery of, 471
  of thymus, 578
    blood-findings in, 616, 617
    clinical signs, 616
    diagnosis, 614
    in goiter, 604
    mechanic theory, 579
    pressure on nerves from, 588
      on trachea from, 586
    Röntgen rays in diagnosis of, 615
      in treatment of, 617
    thymectomy in, 618
      technic, 619
    treatment, 617
      operative, 618
Eosinophilic cells in thymus, 563
Epididymitis, postoperative, 745
Epiphyseal unions, persistence of, in status thymicolymphaticus, 598
Erythrocytes in thymus, 564
Esophagus, dilatation of, diffuse, 3
      diagnosis, 5
      etiology, 3
      treatment, 5
  diverticula of, 189
    Plummer's test for diagnosing, 190
  stenosis of, from diaphragmatic hernia, 236
Ether anesthesia in operations for exophthalmic goiter, 512
      for goiter, 518
Eventration of diaphragm, diaphragmatic hernia and, differentiation, 226
Ewart's crucial test, 650

Exercises, Alexander, after prostatectomy, 372
Exophthalmic goiter, clinical and pathologic aspects, relationship of, 535
  diagnosis, 508
  enlargement of thymus in, 604
  ether anesthesia in operations for, 512
  factors of safety in operating for, 508
  ligation in, 511
  status thymicolymphaticus associated with, 604
Exposure of kidney, incision for, 687
Extramucosal intestinal inflammation, 157
Extremities, 627

FALSE diverticula, 188
  of intestine, 162, 172
Feces, blood in, in diverticulitis of large intestine, 152
  microscopic examination of, method for, 699
Femoral hernia, repair of, from peritoneal side of abdominal wall, 240
Fenwick's classification of functional dyspepsias, 15
Fetal thyroid, 549
Fever in splenic anemia, 458
Fibroids of uterus with cancer, 420
Fibroma of spleen, 445
Fibromyoma of bladder, 355
Fistula, urinary, after prostatectomy, 374
Flagellate protozoa in gastric contents, 51
Foot, bone tumor of, 678
  sole of, sesamoid bones in, 680
Forceps, Lower's, 479
Foreign proteid, 64
Fracture of patella, Blake's operation for, 677
Fractures, open treatment, 673
Fresh tissues, microscopic examination of, for diagnosis of early cancer, 721
Fulguration in tumors of bladder, 351, 365
    results, 367
Function of prostate gland, 368
Functional dyspepsias, 15
  results in prostatectomy, 368
Furunculosis, postoperative, 745
Fused kidney, 250

GALL-BLADDER, disease of, and enlargement of spleen, etiologic relationship, 462
    associated with dyspepsia, 12
  in ulcer of stomach without food retention, 84
Gastric contents, amebæ in, 53
    flagellate protozoa in, 51
    technic for application of glycyltryptophan test to, 696
      of tryptophan test to, 698
    trichomonas hominis in, 51
  extracts, blood in, relation of, to glycyltryptophan test, 30, 31
    relation of, to tryptophan test, 30, 31
    microscopic examination of, method for, 699
Gastro-intestinal tract, cancer of, operative results in, 135
    diverticula of, 188
      surgical importance, 188
Gastrojejunostomy, posterior, management of opening in transverse mesocolon in completing, 683
Gaucher spleen, diagnosis, 445
    pathology, 491
General papers, 703
Genitals in status thymicolymphaticus, 601
German surgery, observations on, 791
Germany, hospitals of, visit to, 780
Gersuny twist for control of bowel, 199
Glands, ductless, 441
  wonder, 513
Glycyltryptophan splitting agent in saliva, 33

Glycyltryptophan test in cancer of stomach, 18, 19, 25
  in diseases of stomach, 18, 27
  in duodenal ulcer, 26
  in ulcer of stomach, 25
  relation of bile to, 30
    of blood in gastric extracts to, 30, 31
    to acidity, 27
    to organic acid, 29
  technic for application of, to gastric contents, 696
Goiter, 513
  enlargement of thymus in, 604
  ether anesthesia in operations for, 518
  etiology of, 516
  exophthalmic, clinical and pathologic aspects, relationship of, 525
    diagnosis of, 508
    ether anesthesia in operations for, 512
    factors of safety in operating for, 508
    ligation in, 511
    status thymicolymphaticus associated with, 604
  of adolescence, 517
    iodin in, 517
  operation for, ether anesthesia in, 518
    prevention of tetany in, 523
    technic, 518
  pathologic anatomy, 536
  relation of, to its structural and physiologic units, 546
  status thymicolymphaticus associated with, 604
Graduate instruction in medicine, 770
Grafting of cancer, 705
Graves' disease. See *Exophthalmic goiter.*
Grawitzian tumors, embryogenetic relationships of, 307
Grocco's paravertebral triangle of dulness, 640
    auscultatory phenomena over, 652
    constancy, 652
Grocco's paravertebral triangle of dulness, in double effusions, 653
    inability to demonstrate, 653
    method of determining, 648
    palpation in, 652
    physical characteristics, 649
    position in thorax, 652
    theories as to mode of production, 643
Growth of thymus, 565
Gumma of thymus, 576
Gums, condition of, relation, to peptid-splitting power of saliva, 40
Gurd's modification of Noguchi reaction, 759

HAMBURG, surgical work at, 781
Hanot's cirrhosis, splenic enlargement in, 446
Head, 627
Hematemesis in splenic anemia, 455
Hematuria in malignant tumors of kidney, 289
  in tumors of bladder, 356
Hemochromatosis, enlargement of spleen in, 446
Hemolytic system in Noguchi reaction, 752
Hemorrhage in thymus, 574
  in ulcer of stomach without food retention, 75, 76, 88
  of thyroid, 530
Hemorrhagic cysts of ovary, 393, 402
Hernia, 223
  diaphragmatic, diagnosis of, 225
      x-rays in, 228
    elevation of diaphragm and, differentiation, 226
    esophageal stenosis from, 236
    hydropneumothorax and, differentiation, 235
    pneumothorax and, differentiation, 234
    pyloric stenosis from, 236
    pyopneumothorax and, differentiation, 235

Hernia, diaphragmatic, subdiaphragmatic pyopneumothorax and, differentiation, 235
  femoral, repair of, from peritoneal side of abdominal wall, 240
  inguinal, occurrence of, after appendectomy, 242
    right, repair of, from peritoneal side of abdominal wall, 240
  mucosæ, 162, 172
  repair of, from peritoneal side of abdominal wall, 240
  umbilical, repair of, from peritoneal side of abdominal wall, 241
Histology of thymus, 561
Hochenegg's operation for cancer of rectum, 212
Hodgkin's disease, splenic enlargement in, 446
Holland, hospitals of, visit to, 788
Hollowing of thymic parenchyma, 573
Horseshoe kidney, 250
    classification, 271
    diagnosis, 274
    hydronephrosis in, 272
    Mayo's incision in operation for, 277
    pain in, 274
    pyonephrosis in, 272
    sex frequency, 273
    surgery of, 265
    tuberculosis in, 272
    x-rays in diagnosis of, 251
Hospitals of Austria, visit to, 780
  of Germany, visit to, 780
  of Holland, visit to, 788
  of Switzerland, visit to, 780
Hyaline degeneration in thyroid, 533
Hydronephrosis in horseshoe kidney, 272
Hydropneumothorax, diaphragmatic hernia and, differentiation, 235
Hyperemia of thymus, 574
  of thyroid, 530
Hypernephroma of kidney, 289
    embryogenetic relationship of, 307
Hyperplasia, chronic lymphocytic, of spleen, pathology, 488
Hyperplasia, inflammatory lymphatic, 99
  of spleen, primary (chronic) diffuse, pathology, 500
  of thyroid, 531
  thymic, 593. See also *Status thymicolymphaticus.*
Hypertrophic colloid thyroid, 552
  parenchymatous thyroid, 552
Hypertrophy of prostate, prostatectomy for, 376
      functional results after, 368
  of thyroid, 530

ILEOCECAL orifice, contraction of, as cause of intestinal phenomena, 143
Ileum, diverticula of, 194
Incision for exposure of kidney, 687
  Mayo's, in operation for horseshoe kidney, 277
  McBurney's, in operation for appendicitis, right inguinal hernia after, 242
Incontinence of urine after prostatectomy, 371
Infarcts as cause of splenic enlargement, 445
Infections, acute, of childhood, enlargement of spleen in, 443
  postoperative, 739
Infectious diseases of childhood, effect of, on thymus, 574
  splenomegaly, 463
Inflammation, intestinal, extramucosal, 157
  of thymus, 575
  of thyroid, 530
Inflammatory lymphatic hyperplasia, 99
Inguinal hernia, repair of, from peritoneal side of abdominal wall, 240
    right, occurrence of, after appendectomy, 242
Injection and lavage of pelves of kidneys and ureters, apparatus for, 689
Intestinal inflammation, extramucosal, 157

Intestine, Gersuny twist for control of, 199
  large, adhesions in, 144
    anatomy of, 136
    cancer of, operative results in, 135
    diverticula of, 192, 194
      Bloodgood's operation for, 201
      cancer grafted on, 200
      clinical diagnosis, 183
      content, 159
      diagnosis, differential, 200
      etiology, 156
      Mikulicz's operation for, 201
      openings, 159
      operation in, 201
      pathogenesis, 156, 173
      pathologic examination, 184
      shape, 158
      size, 158
      structure, 158
    diverticulitis of, age, 150
      bladder examination in, 152
      blood count in, 152
      blood in stools in, 152
      constipation in, 151
      diagnosis, 148
        preoperative, 149
      diarrhea in, 151
      etiology, 171
      leukocytosis in, 152
      manual examination in, 152
      nutrition, 150
      occupation, 150
      pain in, 150
      rectal examination in, 152
      sex, 150
      temperature in, 152
      vomiting in, 151
      weight, 150
    false diverticula, 162
    lymphatics of, 139
    surgery of, disputed problems associated with, 142
  small, anatomy of, 135
    cancer of, operative results in, 135
    lymphatics of, 139

Involution of thymus, 565
    accidental, 567
Iodin content of thyroid, 543
  in goiter of adolescence, 517
Iodothyrin, 543, 547
Iodothyroglobulin, 543, 547
Irritation, chronic, as factor in cause of cancer, 716, 722

JAUNDICE in splenic anemia, 459
  splenic enlargement in, 447
Jejunostomy, 129
  for accidental injuries to cancerous stomach, 133
  in ulcer of stomach, 131
  indications for, 129
  technic, 129
Jejunum, diverticula of, 194

KALA-AZAR, splenic enlargement in, 447
Kidney and ureters, pelves of, apparatus for injection and lavage of, 689
  atrophic, 256
  cancer of, 289
  capsule of, tumors, embryogenetic relationships, 311
  congenital anomalies in, clinical diagnosis, 249
    single, 254
      palpation in diagnosis of, 255
  cortex of, tumors of, embryogenetic relationships of, 305
  ectopic, 258
  embryoma of, 289
  enlargement of, and enlargement of spleen, differentiation, 442
  exposure of, incision for, 687
  function of, estimation, in malignant tumors of kidney, 297
  fused, 250
  Grawitzian tumors of, embryogenetic relationships, 307
  horseshoe, 250
    classification, 271
    diagnosis, 274

Kidney, horseshoe, hydronephrosis in, 272
    Mayo's incision in operation for, 277
    pain in, 274
    pyonephrosis in, 272
    sex frequency, 273
    surgery of, 265
    tuberculosis in, 272
    x-rays as aid in diagnosis, 251
  hypernephroma of, 289
    embryogenetic relationships, 307
  malignant tumors of, 289
      circulatory disturbances in, 292
      cough in, 295
      cystoscopic data in, 295
        inspection in, 295
      diagnosis, differential, 293
      estimation of renal function in, 296
      hematuria in, 289
      inoperable, 300
      nephrectomy in, results of, 302
      pain in, 291
      palpation in, 291
      pyelography in, 297
      sex in, 295
      tumor mass in, 290
      ureteral catheter in, 296
      urinalysis in, 292
  mesothelioma of, 289
    embryogenetic relationships, 307
  palpation of, in malignant tumors, 291
  pelvic, 258
  pelvis of, duplicated, 260
    tumors of, embryogenetic relationships, 304
  sarcoma of, 289
  sigmoid, 252
  single, surgery of, 265
  tuberculosis of, examination of urine in, 282
    nephrectomy for, without drainage, 686
    results of early diagnosis of, 280
  tumors of, embryogenetic relationships of, 303, 304, 321
Kink, Lane's, 145
Kocher's operation for prolapse of uterus, 435
Kraske's operation for cancer of rectum, 210

LANE's kink, 145
Lannier-Hackerman area, 189
Lateral thyroid anlagen, 529
Lavage and injection of pelves of kidneys and ureters, apparatus for, 689
  of pelves of kidneys and ureters, apparatus for, 689
Laying of corner-stone, 803
Leukemia, enlargement of spleen in, 445
  myelogenous, enlargement of spleen in, 471
Leukocyte count in splenic anemia, 455
Leukocytosis in diverticulitis of large intestine, 152
Ligament, costocolic, 136
Ligation in exophthalmic goiter, 511
Lilienthal's method of colostomy in cancer of rectum, 206
Lingual thyroid, 514
Lipoma of thymus, 578
Liver, cirrhosis of, in splenic anemia, 459
    primary, 446
    splenic enlargement in, 446
  common and hepatic ducts, diverticula of, 193
  function of, 469
  syphilis of, associated with dyspepsia, 14
Living pathology, contributions of the nineteenth century to, 711
Lobar pneumonia, postoperative, 742, 743
Lobes of thymus, 564
Lower's forceps, 479
Lutein cells in ovarian cysts, 395
  test in diagnosis of syphilis, 761
Lymphatic glands, regional, involvement of, in cancer of stomach, 90–128

Lymphatic hyperplasia, inflammatory, 99
  leukemia, splenic enlargement in, 445
Lymphatics of large intestine, 139
  of small intestine, 139
  of stomach, 138
Lymphatism, 578. See also *Status thymicus*.
Lymphocytes, thymic, 561
Lymphocytic hyperplasia, chronic, of spleen, pathology, 488
Lymphoma of spleen, diagnosis, 444
Lymphosarcoma of thymus, 578

Malaria, enlargement of spleen in, 443
  in Northern States, 763
  in splenic anemia, 459
Malignant disease, grafting and traumatic dissemination of cancer in operations for, 705
  ovarian cysts, 393
  tumors of kidney, 289
    circulatory disturbances in, 292
    cough in, 295
    cystoscopic data in, 295
      inspection in, 295
    diagnosis, differential, 293
    hematuria in, 289
    inoperable, 300
    nephrectomy in, results of, 302
    pain in, 291
    palpation in, 291
    pyelography in, 297
    renal function in, 296
    sex in, 295
    tumor mass in, 290
    ureteral catheter in, 296
    urinalysis in, 292
Mayo's incision in operation for horseshoe kidney, 277
McBurney's incision in operation for appendicitis, right inguinal hernia after, 242
Meatotomy, ureteral, experimental technic, 329
      results of, 332
  feasibility of, 324
    safety of, 326
Meckel's diverticulum, 194
Medicine, graduate instruction in, 770
Melena in ulcer of stomach without food retention, 82, 88
Mesocolon, transverse, management of opening in, in completing the operation of posterior gastrojejunostomy, 683
Mesothelioma of kidney, 289
    embryogenetic relationships of, 307
Microscopic examination of feces, method for, 698
    of fresh tissues for diagnosis of early cancer, 721
    of gastric extracts, method for, 699
Micturition, frequency of, after prostatectomy, 370
Mikulicz's operation for diverticula of large intestine, 201
Mirror, operating-room, 693
Mouth-washes, effect of, on peptid-splitting power of saliva, 41
Movable spleen, diagnosis, 442
    surgery of, 474
Muscle resistance sign, 640
Myasthenia gravis, status thymicolymphaticus and, relationship, 603
Myelogenous leukemia, enlargement of spleen in, 445, 471

Narrowness of aorta in status thymicolymphaticus, 600
Nasal conditions, relation of, to anaphylaxis and asthma, 635
Nasopharynx, condition of, relation, to peptid-splitting power of saliva, 40
Nephrectomy in malignant tumors of kidney, results, 302
  without drainage for tuberculous kidney, 686
Nerves, pressure on, from thymic enlargement, 588
Nervous system, syphilis of, cytodiagnosis as aid in diagnosis of, 762

Neubauer and Fischer's test in cancer of stomach, 19
Noguchi reaction, 752
    amboceptor in, 752
    antigen in, 754
    complement for, 753
    Emery's modification, 760
    Gurd's modification, 759
    hemolytic system in, 752
    patient's serum in, 753
    Stitt's modification, 760
Northern States, malaria in, 763

OPEN treatment of fractures, 673
Operating-room mirror, 693
Operations, surgical, acute dilatation of stomach after, 745
    bronchitis after, 741, 743
    bronchopneumonia after, 742, 743
    cellulitis after, 745
    complications after, 738
    epididymitis after, 745
    furunculosis after, 745
    infections after, 739
    lobar pneumonia after, 742, 743
    orchitis after, 745
    phlebitis after, 742
    pleurisy after, 741, 743
    pulmonary complications after, 741
        embolism after, 741
    rash after, 744
    scarlatina after, 745
    thrombophlebitis after, 742, 744
    tonsillitis after, 745
Oral conditions, relation, to peptid-splitting power of saliva, 39
Orchitis, postoperative, 745
Organic acid, relation of glycyltryptophan test to, 29
        of tryptophan test to, 29
Ovary, cystadenoma of, 399, 405
    cysts of, benign, 393
        dermoid, 393
        hemorrhagic, 393, 402
        linings of, 394, 395
        lutein cells in, 394, 395
Ovary, cysts of, malignant, 393
        simple, 397
        tarry, 401
    dermoid cysts of, 393
    hemorrhagic cysts of, 393, 402
    tarry cysts of, 401

PAIN in diverticulitis of large intestine, 150
    in horseshoe kidney, 274
    in malignant tumors of kidney, 291
    in splenic anemia, 458
    in tumors of bladder, 358
    in ulcer of stomach without food retention, 69–73, 87
Palpation in diagnosis of congenital single kidney, 255
    in Grocco's paravertebral triangle of dulness, 652
    in malignant tumors of kidney, 291
Paltauf's theory of status thymicolymphaticus, 596
Papers, general, 703
Papilloma of bladder, 343, 355
Paravertebral triangle of percussion dulness, auscultatory phenomena over, 652
        constancy of, 652
        diagnostic significance, 640
        in double effusions, 653
        inability to demonstrate, 653
        method of determining, 648
        palpation in, 652
        physical characteristics, 649
        position in thorax, 652
        theories as to mode of production, 643
Parenchymatous thyroid, 552
Parenteral digestion, 768
Parovarian cysts, 393
Patella, fracture of, Blake's operation for, 677
Pathology, living, contributions of the nineteenth century to, 711
    of thymus, 573
    postmortem, 712

Pelves of kidneys and ureters, injection and lavage of, apparatus for, 689
Pelvic kidney, 258
Pelvis, renal, duplicated, 260
    tumors of, embryogenetic relationships of, 304
Peptid-splitting agent in human blood-serum, 768
  power of saliva, 33, 35
      effect of alphozone solutions on, 44, 45
        bacteria on, 46, 48
        of centrifugalization on, 37
        of chemic solutions on, 43–46
        of chloroform solutions on, 45
        of mouth-washes on, 41
        of temperature on, 41–43
        of tobacco on, 40
      relation of condition of gums to, 40
        of condition of nasopharynx to, 40
        of condition of teeth to, 39
          of tonsils to, 40
        of oral conditions to, 39
        of reaction of saliva to, 38
      routine procedure for observation, 34
Percussion dulness, paravertebral triangle of, auscultatory phenomena over, 652
        constancy, 652
        diagnostic significance, 640
        in double effusions, 653
        inability to demonstrate, 653
        method of determining, 648
        palpation in, 652
        physical characteristics, 649
        position in thorax, 652
        theories as to mode of production, 643
Perforation in ulcer of stomach without food retention, 73
Peridiverticulitis, 179, 185
Perineum, repair of, Tait's operation for, 436
Perisplenitis, 441
Peritendineum, 666
Peritoneal side of abdominal wall, repair of hernia from, 240
Pernicious anemia associated with dyspepsia, 15
    enlargement of spleen in, 445
    splenomegaly in, 467
Pharyngo-esophageal diverticulum, 189
Phlebitis, postoperative, 742
Physiology of thymus, 568
Plasma cells in thymus, 564
Pleural effusion, double, Grocco's sign in, 653
    Grocco's sign in, 640
Pleurisy, postoperative, 741, 743
Plummer's test in diagnosis of esophageal diverticulum, 190
Pneumonia, lobar, postoperative, 742, 743
Pneumothorax, diaphragmatic hernia and, differentiation, 234
Polycythemia, enlargement of spleen in, 445
Porro-cesarean section, 422
Postanal dermoid, 658
    diagnosis, 664
Postmortem pathology, 712
Postnatal thyroid, 549
Postoperative bronchitis, 741, 743
  bronchopneumonia, 742, 743
  cellulitis, 745
  complications, 738
  dilatation of stomach, 745
  embolism, 727
    causes, 732
    prevention, 733, 736, 737
  epididymitis, 745
  furunculosis, 745
  infections, 739
  lobar pneumonia, 742, 743
  orchitis, 745
  phlebitis, 742
  pleurisy, 741, 743
  pulmonary complications, 741
    embolism, 741
  scarlatina, 745

Postoperative surgical rash, 744
  thrombophlebitis, 742, 744
  tonsillitis, 745
Prague, surgical work at, 783
Precancerous conditions, 722
Pressure diverticula of esophagus, 189
  on nerves from thymic enlargement, 588
  on trachea from thymic enlargement, 586
Prolapse of uterus during child-bearing period, treatment of, 430
      middle age, treatment of, 433
    in elderly women, treatment of, 434
    Kocher's operation for, 435
    surgical treatment, 429
    vaginopelvic fixation operation for, 434
  of walls of vagina, surgical treatment, 429
Prostate gland and testicles, relation between, 368
    function of, 368
    hypertrophy of, prostatectomy for, 376
      functional results after, 368
    involvement of, in tumors of bladder, 346
Prostatectomy, 376
  Alexander exercises after, 372
  effect of, on sexual power, 369
  first stage, 376
  frequency of micturition after, 370
  functional results in, 368
  incontinence of urine after, 371
  second stage, 377
  suprapubic, disadvantages of, 378
    technic of, 378
  urinary control after, 371
    fistula after, 374
Proteid, foreign, 64
Protozoa, flagellate, in gastric contents, 51
Pseudoleukemia, splenic enlargement in, 445
Pulmonary complications, postoperative, 741
Pulmonary embolism, postoperative, 741
  tuberculosis associated with dyspepsia, 14
Pulsion diverticula of esophagus, 189
Pyelography in malignant tumors of kidney, 297
Pyloric stenosis from diaphragmatic hernia, 236
Pyonephrosis in horseshoe kidney, 272
Pyopneumothorax, diaphragmatic hernia and, differentiation, 235
  subdiaphragmatic, diaphragmatic hernia and, differentiation, 235

QUÉNU-TUTTLE perineal resection for cancer of rectum, 209

RAM-WHITE operation, 368
Reaction, Noguchi, 752
    amboceptor for, 752
    antigen in, 754
    complement for, 753
    Emery's modification, 760
    Gurd's modification, 759
    hemolytic system in, 752
    patient's serum in, 753
    Stitt's modification, 760
Rectal examination in diverticulitis of large intestine, 152
Rectocele, treatment of, 437
Rectosigmoid, cancer of, operability, 206
    juncture, 143
    radical operation for, 203
      first stage, 218
      second stage, 218
Rectum, anatomy of, 136
  cancer of, abdominal operation in one stage, 212
    abdominoperineal operation in one stage, 212
    Cripps' perineal resection for, 209
    Hochenegg's operation for, 212
    Kraske's operation for, 310

Rectum, cancer of, operability, 206
operations for, local, 208
through perineum or posterior sacral incision in single stage, 208
operative results in, 140
preliminary colostomy with secondary posterior resection, 217
Quénu-Tuttle perineal resection for, 209
radical operation for, 203
colostomy in, 206
first stage, 218
Lilienthal's method of colostomy in, 206
principles in technic, 204
second stage, 218
tube operation, 214
diverticulum of, 196
first portion, 203
second part, 136, 203
third part, 136, 204
Refraction, errors of, 629
Regeneration of tendons, 665
of thymus, 567
Regional lymphatic glands, involvement of, in cancer of stomach, 90–128
Renal blastema, 266
capsule, tumors of, embryogenetic relationships, 311
cortex, tumors of, embryogenetic relationships of, 305
function, estimation of, in malignant tumors of kidney, 296
pelvis, duplicated, 260
tumors of, embryogenetic relationships of, 304
tuberculosis, examination of urine in, 282
nephrectomy for, without drainage, 686
results of early diagnosis of, 280
Reticulum cells in thymus, 561
Rickets, enlargement of spleen in, 443
Röntgen rays. See *x-rays.*

SACROCOCCYGEAL sinus, 658
diagnosis of, 664
Saliva, collection of, for testing, 34
glycyltryptophan splitting agent in, 33
peptid-splitting power, 33, 35
effect of alphozone solutions on, 44, 45
of bacteria on, 46, 48
of centrifugalization on, 37
of chemic solutions on, 43–46
of chloroform on, 45
of mouth-washes on, 41
of temperature on 41–43
of tobacco on, 40
relation of condition of gums to, 40
of nasopharynx to, 40
of teeth to, 39
of tonsils to, 40
of oral conditions to, 39
of reaction of saliva to, 38
routine procedure for observation, 34
reaction of, relation to, peptid-splitting power of saliva, 38
Sänger's method of cesarean section, 424, 425
Sarcoma of kidney, 289
of spleen, diagnosis, 444
surgery, 475
of thymus, 578
Scarlatina, postoperative, 745
Secretion of thyroid gland, 514
retention of, by thyroid gland, 532
Seeding of cancer, 705
Serum, blood-, human, peptid-splitting agent in, 768
patient's, in Noguchi reaction, 753
Sesamoid bones in sole of foot, 680
Sex in malignant tumors of kidney, 295
Sexual power, effect of prostatectomy on, 369
Sigmoid, diverticulum of, 195
kidneys, 252
Sign, Grocco's, 640
auscultatory phenomena over, 652
constancy of, 652
in double effusions, 653

Sign, Grocco's, inability to demonstrate, 653
    method of determining, 648
    palpation in, 652
    physical characteristics, 649
    position in thorax, 652
    theories as to mode of production of, 643
  muscle resistance, 640
Single kidney, surgery of, 265
Sinus, sacrococcygeal, 658
    diagnosis of, 664
Skin-perineum operation, 436
Smithies' modification of glycyltryptophan and tryptophan tests, 20
Sole of foot, sesamoid bones in, 680
Spinal column, 627
Spleen, cancer of, 445
  chronic lymphocytic hyperplasia of, pathology, 488
  cystic, diagnosis of, 445
  cysts of, 475
  endothelioma of, Gaucher type, diagnosis, 445
  endothelium of, primary proliferation of, 491
  enlargement of, abscess as cause, 445
    and enlargement of kidney, differentiation, 442
    conservative surgery in, 473
    diagnosis of diseases associated with, 441
    gall-bladder disease and, etiologic relationship, 462
    in acute infections of childhood, 443
    in cirrhosis of liver, 446
    in Hanot's cirrhosis, 446
    in hemochromatosis, 446
    in Hodgkin's disease, 446
    in jaundice, 447
    in kala-azar, 447
    in leukemia, 445
    in malaria, 443
    in myelogenous leukemia, 471
    in pernicious anemia, 445, 467
    in polycythemia, 445
    in rickets, 443
Spleen, enlargement of, in splenic anemia, 451
    in tuberculosis, 443
    in typhoid fever, 443
    in Weil's disease, 447
    infarcts as cause, 445
    infectious, 463
    pathology, 482
    in pseudoleukemia, 445
    surgery of, 471
  fibroma of, 445
  function of, 469
  Gaucher, pathology of, 491
  hyperplasia of, primary (chronic) diffuse, pathology, 500
  lymphoma of, diagnosis, 444
  movable, diagnosis of, 442
    surgery of, 474
  new-growths of surgery, 475
  sarcoma of, diagnosis, 444
    surgery, 475
  surgery of, 469
  syphilis of, diagnosis, 444
  tuberculosis of, 466
  tumors of, surgery, 475
  wandering, 466
    diagnosis of, 442
    surgery of, 474
Splenectomy, clinical observations concerning, 449
  line of incision for, 476
  mortality following, 480
  operative mortality, 462
  technic of, 475
Splenic anemia, 446, 449, 450, 472
    blood-findings in, 455–457, 472
    cirrhosis of liver in, 459
    contour and position of spleen in, 451–454
    diarrhea in, 458
    enlargement of spleen in, 451
    fever in, 458
    hematemesis in, 455
    jaundice in, 459
    leukocyte count in, 455
    malaria in, 459
    pain in, 458

Splenic anemia, pathology, 487
Splenitis, chronic, pathology of, 500
Splenomegaly. See *Enlargement of spleen.*
  diagnosis of various forms, 441
States, Northern, malaria in, 763
Status lymphaticus, 594
    associated with goiter, 604
    pressure on nerves from, 588
  thymicolymphaticus, 593
    Addison's disease and, relationship, 602
    adrenals in, 600
    associated with exophthalmic goiter, 604
      with goiter, 604
    genitals in, 601
    myasthenia gravis and, relationships, 603
    narrowness of aorta in, 600
    persistence of epiphyseal union in, 598
    tumors associated with, 601
  thymicus, 578
    blood-findings in, 616, 617
    clinical signs, 616
    diagnosis, 614
    mechanic theory, 579
    pressure on trachea from, 586
    Röntgen rays in diagnosis of, 615
      in treatment of, 617
    thymectomy in, 618
      technic, 619
    treatment, 617
      operative, 618
Stenosis of esophagus from diaphragmatic hernia, 235
  pyloric, from diaphragmatic hernia, 236
Stitt's modification of Noguchi reaction, 760
Stomach, anatomy of, 135
  cancer of, accidental injuries to stomach during exploration, jejunostomy for, 133
    associated with dyspepsia, 13
    glycyltryptophan test in, 18, 19, 25
Stomach, cancer of, involvement of regional lymphatic glands in, 90–128
    Neubauer and Fischer's test for, 19
    operative results in, 135
    tryptophan test in, 19, 25
    Weinstein's test in, 19
  dilatation of, acute, postoperative, 745
  diseases of, glycyltryptophan test in, 18, 27
    tryptophan test in, 18, 27
  diverticula of, 191
  lymphatics of, 138
  syphilis of, associated with dyspepsia, 14
  ulcer of, associated with dyspepsia, 12
    duodenal ulcer and, differentiation, 12
    glycyltryptophan test in, 25
    jejunostomy in, 131
    tryptophan test in, 25
    without food retention, 66
      acidity in, 77–83, 88
      age in, 67
      anemia in, 68
      appendix alterations in, 84
      appetite in, 68
      bowels in, 68
      character of complaint, 68
      cholecystitis in, 84
      cholelithiasis in, 84
      dietetic errors in, 67
      gall-bladder in, 84
      habits in, 67
      hemorrhage in, 75, 76, 88
      loss of weight in, 68
      melena in, 82, 88
      nationality in, 67
      nutrition in, 68
      occupation in, 67
      operative findings in, 84, 89
        procedures in, 85, 89
      pain in, 69–73, 87
      perforation in, 73
      previous disorders of digestion in, 69
        infectious diseases in, 68

Stomach, ulcer of, without food retention, secondary operations in, 86
      symptoms, 69
      test-meal findings in, 76, 88
      vomiting in, 74, 75, 88
Subdiaphragmatic pyopneumothorax, diaphragmatic hernia and, differentiation, 235
Suprapubic prostatectomy, disadvantages, 378
   technic, 378
Suprarenal gland, tumors of, embryogenetic relationships of, 303, 313, 322
Surgical operations, acute dilatation of stomach after, 745
   bronchitis after, 741, 743
   bronchopneumonia after, 742, 743
   cellulitis after, 745
   complications after, 738
   epididymitis after, 745
   furunculosis after, 745
   infections after, 739
   lobar pneumonia after, 742, 743
   orchitis after, 745
   phlebitis after, 742
   pleurisy after, 741, 743
   pulmonary complications after, 741
      embolism after, 741
   rash after, 744
   scarlatina after, 745
   thrombophlebitis after, 742, 744
   tonsillitis after, 745
  rash, 744
Suture of tendons, 665
Switzerland, hospitals of, visit to, 780
Syphilis, butyric acid test in diagnosis of, 761
  lutein test in diagnosis of, 761
  Noguchi reaction in diagnosis of, 752
  of liver associated with dyspepsia, 14
  of nervous system, cytodiagnosis as aid in diagnosis of, 762
  of spleen, diagnosis, 444
  of stomach associated with dyspepsia, 14
  of thymus, 575
Syphilis of thymus, cyst in, 576
    Dubois abscess in, 576
  Weil's cobra-venom test for diagnosis of, 760
Syphilitic antibody, 755

TAIT'S operation for repair of perineum, 436
Tarry cysts of ovary, 401
Technic, 681
Teeth, condition of, relation, to peptid-splitting power of saliva, 39
Temperature, effect of, on peptid-splitting power of saliva, 41–43
  in diverticulitis of large intestine, 152
Tendons, regeneration of, 665
Test, butyric acid, in diagnosis of syphilis, 761
  crucial, of Ewart, 650
  glycyltryptophan, in cancer of stomach, 18, 19, 25
    in diseases of stomach, 18, 27
    in duodenal ulcer, 26
    in ulcer of stomach, 25
    relation of bile to, 30
      of blood in gastric extracts to, 30, 31
      to acidity, 27
      to organic acid, 29
    technic for application of, to gastric contents, 696
  lutein, in diagnosis of syphilis, 761
  Neubauer and Fischer's, for cancer of stomach, 19
  Noguchi, 752. See also *Noguchi reaction.*
  Plummer's, in diagnosis of esophageal diverticulum, 190
  tryptophan, in cancer of stomach, 19, 25
    in diseases of stomach, 18, 27
    in duodenal ulcer, 26
    in ulcer of stomach, 25
    relation of bile to, 30
      of blood in gastric extracts to, 30, 31

Test, tryptophan, in relation to acidity, 28
    to organic acid, 29
  technic for application of, to gastric contents, 698
 Weil's cobra-venom, for diagnosis of syphilis, 760
 Weinstein's, in cancer of stomach, 19
Test-meal findings in ulcer of stomach without food retention, 76, 88
Testicle, tumors of, embryogenetic relationships of, 303, 318, 322
Testicles and prostate gland, relation between, 368
Tetany, prevention of, in goiter operations, 523
Thorax, 627
Thrombophlebitis, postoperative, 742, 744
Thymectomy, effect of, 569–572
  on blood formation, 572
 in enlargement of thymus, 618
   technic, 619
Thymic asthma, 578
 death, 559, 578
 diphtheria, 575
 extract, 569
  influence of, in clot-formation, 573
 hyperplasia, 593. See also *Status thymicolymphaticus.*
 lymphocytes, 561
 persistence, 565, 593. See also *Status thymicolymphaticus.*
Thymus, abscess of, 575
 absence of, 574
 accidental involution of, 567
 anatomy of, 564
  topographic, 579
 and thyroid, relationship, 561
 cancer of, 577
 cells of, 561
 cysts of, 578
  in syphilis of thymus, 576
 development of, 560
 diseases of, 573
 effect of infectious diseases of childhood on, 574
Thymus, embryology of, 560
 enlargement of, 578
  blood-findings in, 616, 617
  clinical signs, 616
  diagnosis, 614
  in goiter, 604
  mechanic theory, 579
  pressure on nerves from, 588
   on trachea from, 586
  Röntgen rays in diagnosis of, 615
    in treatment of, 617
  thymectomy in, 618
   technic, 619
  treatment, 617
   operative, 618
 eosinophilic cells in, 563
 erythrocytes in, 564
 growth and involution, 565
 gumma of, 576
 hemorrhage in, 574
 histology of, 561
 hollowing of parenchyma of, 573
 hyperemia of, 574
 inflammation of, 575
 involution of, 565
  accidental, 567
 lipoma of, 578
 lobes of, 564
 lymphocytes of, 561
 lymphosarcoma of, 578
 pathology of, 573
 persistence of, 565
 physiology of, 568
 plasma cells in, 564
 red blood-corpuscles in, 564
 regeneration of, 567
 removal of, effect of, 569–572
   on blood formation, 572
 reticulum cells in, 561
 sarcoma of, 578
 surgical importance of, 556
 syphilis of, 575
  cyst in, 576
  Dubois abscess in, 576
 thyroid and, relationship, 561
 topography of, 579
 toxicity of, 569

- Thymus, tuberculosis of, 575
  - tumors of, 576
    - classes, 577
  - weight of, 567
- Thyroglossal duct cyst, 514
- Thyroid anlagen, lateral, 529
  - gland, adenoma of, 531
    - adenomatosis of, 531
    - amyloid degeneration in, 533
    - and thymus, relationship, 561
    - atrophy of, 532
    - calcareous degeneration, 533
    - chemic nature, 543
    - colloid degeneration, 533
    - development of, 513, 529
    - fetal, 549
    - hemorrhage of, 530
    - hyaline degeneration, 533
    - hyperemia of, 530
    - hyperplasia of, 531
    - hypertrophic colloid, 552
      - parenchymatous, 552
    - hypertrophy of, 530
    - inflammation of, 530
    - iodin content, 543
    - of mother, influence of, on growth of child in uterus, 514
    - parenchymatous, 552
    - postnatal 549
    - retention of secretion by, 532
    - retrogressive changes in, 532
    - secretion of, 514
    - terminal degenerations, 533
    - thymus and, relationship, 561
    - transplantation of, 515
    - weight of, 515
  - lingual, 514
- Thyroidectomy, technic of, 518
- Tissues, fresh, microscopic examination of, for diagnosis of early cancer, 721
- Tobacco, effect of, on peptid-splitting power of saliva, 40
- Tonsillitis, postoperative, 745
- Tonsils, condition of, relation to peptid-splitting power of saliva, 40
- Topographic anatomy of thymus, 579
- Toxicity of thymus, 569
- Trachea, pressure on, from enlargement of thymus, 586
- Traction diverticula of esophagus, 189
- Transplantation of thyroid gland, 515
- Traumatic dissemination of cancer, 705
- Triangle, Grocco's, 640
  - auscultatory phenomena over, 652
  - constancy of, 652
  - in double effusions, 653
  - inability to demonstrate, 653
  - method of determining, 648
  - palpation in, 652
  - physical characteristics, 649
  - position in thorax, 652
  - theories as to mode of production of, 643
- Trichomonas hominis in gastric contents, 51
- Tryptophan test in cancer of stomach, 19, 25
  - in diseases of stomach, 18, 27
  - in duodenal ulcer, 26
  - in ulcer of stomach, 25
  - relation of bile to, 30
    - of blood in gastric extracts to, 30, 31
    - to acidity, 28
    - to organic acid, 29
  - technic for application of, to gastric contents, 698
- Tuberculosis, enlargement of spleen in, 443
  - in horseshoe kidney, 272
  - of kidney, examination of urine in, 282
    - nephrectomy for, without drainage, 686
    - results of early diagnosis of, 280
  - of spleen, 466
  - of thymus, 575
  - pulmonary, associated with dyspepsia, 14
  - urinary, results of early diagnosis of, 280
- Tübingen, surgical work at, 787
- Tumors associated with status thymicolymphaticus, 601

Tumors, bone, of foot, 678
  Grawitzian, embryogenetic relationships of, 307
  malignant, of kidney, 289
    circulatory disturbances in, 292
    cough in, 295
    cystoscopic data in, 295
      inspection in, 295
    diagnosis, differential, 293
    estimation of renal function in, 296
    hematuria in, 289
    inoperable, 300
    nephrectomy in, results of, 302
    pain in, 291
    palpation in, 291
    pyelography in, 297
    sex in, 295
    tumor mass in, 290
    ureteral catheter in, 296
    urinalysis in, 292
  of adrenal gland, embryogenetic relationships of, 303, 313, 322
  of bladder, 353
    anatomic findings, 354
    cystoscopic examination in, 345
    diagnosis, 360
    electricity in, 351, 365
    etiology, 354
    frequency, 353
    fulguration in, 351, 365
      results, 367
    hematuria in, 356
    involvement of prostate in, 346
    pain in, 358
    prognosis, 361
    surgical treatment of, methods, 343
      results, 343, 346
    symptoms, 356
    treatment, 363
  of kidney, embryogenetic relationships of, 303, 304, 321
  of renal capsule, embryogenetic relationships of, 311
    cortex, embryogenetic relationships of, 305
Tumors of pelvis, embryogenetic relationships of, 304
  of spleen, surgery of, 475
  of suprarenal gland, embryogenetic relationships of, 303, 313, 322
  of testicle, embryogenetic relationships of, 303, 318, 322
  of thymus, 576
    classes, 577
Typhoid fever, enlargement of spleen in, 443

ULCER, duodenal, associated with dyspepsia, 9
    diagnosis of, 10
    glycyltryptophan test in, 26
    tryptophan test in, 26
    ulcer of stomach and, differentiation, 12
  of stomach associated with dyspepsia, 12
    duodenal ulcer and, differentiation, 12
    glycyltryptophan test in, 25
    jejunostomy in, 131
    tryptophan test in, 25
    without food retention, 66
        acidity in, 77–83, 88
        age in, 67
        anemia in, 68
        appendix alterations in, 84
        appetite in, 68
        bowels in, 68
        character of complaint, 68
        cholecystitis in, 84
        cholelithiasis in, 84
        dietetic errors in, 67
        gall-bladder in, 84
        habits in, 67
        hemorrhage in, 75, 76, 88
        loss of weight in, 68
        melena in, 82, 88
        nationality in, 67
        nutrition in, 68
        occupation in, 67
        operative findings in, 84, 89

Ulcer of stomach without food retention, operative procedures in, 85, 89
  pain in, 69–73, 87
  perforation in, 73
  previous disorders of digestion in, 69
    infectious diseases in, 68
  secondary operations in, 86
  sex in, 67
  symptoms, 69
  test-meal findings in, 76, 88
  vomiting in, 74, 75, 88
Umbilical hernia, repair of, from peritoneal side of abdominal wall, 241
Ureter, atrophy of, 257
  congenital anomalies in, clinical diagnosis, 249, 260
  duplicated, 261
    division of, 262
    partial, 262
Ureteral catheter in malignant tumors of kidney, 296
  meatotomy, experimental technic, 329
    results of, 332
    feasibility of, 324
    safety of, 326
Ureterovesical valve, action of, 332
  function of, 324, 332
Ureters and kidneys, pelves of, apparatus for injection and lavage of, 689
Urinalysis in malignant tumors of kidney, 292
Urinary control after prostatectomy, 371
  fistula after prostatectomy, 374
  tuberculosis, results of early diagnosis of, 280
Urine, examination of, in renal tuberculosis, 282
  incontinence of, after prostatectomy, 371
Urogenital organs, 247
Uterus, cancer of, 415
    age occurring, 419
    fibroids with, 420
    symptoms, 418, 419
  fibroids of, with cancer, 420
Uterus, prolapse of, during child-bearing period, treatment of, 430
    middle age, treatment of, 433
  in elderly women, treatment of, 434
  Kocher's operation for, 435
  surgical treatment, 429
  vaginopelvic fixation operation for 434
Utrecht, surgical work at, 789

VAGINA, walls of, prolapse of, surgical treatment, 429
Vaginal cesarean section, 424
Vaginopelvic fixation operation, 434
Valve, ureterovesical, action of, 332
  function of, 324, 332
Vaselin after removal of drain, 750
Vermiform appendix, alterations in, in ulcer of stomach without food retention, 84
  diverticula of, 194
Vienna, surgical work at, 784
Vomiting in diverticulitis of large intestine, 151
  in ulcer of stomach without food retention, 74, 75, 88

WALLS of vagina, prolapse of, surgical treatment, 429
Wandering spleen, 466
    diagnosis, 442
    surgery of, 474
Weight, loss of, in ulcer of stomach without food retention, 68
  of thymus, 567
  of thyroid gland, 515
Weil's cobra-venom test for diagnosis of syphilis, 760
  disease, splenic enlargement in, 447
Weinstein's test in cancer of stomach, 19
Wölfler's rests, 530
Wonder glands, 513
Wounds, drainage of, 748

Wounds, drainage of, choice of drain, 750
    disadvantages, 748
    indications, 749
    length of time, 750

X-RAYS as aid to diagnosis in malignant tumors of kidney, 297
X-rays in development of living pathology, 719
  in diagnosis of diaphragmatic hernia, 228
    of enlargement of thymus, 615
    of horseshoe kidney, 251
    in treatment of enlargement of thymus, 617

311387

Mayo

B111
M3
v.4

BIOLOGY
LIBRARY
G

UNIVERSITY OF CALIFORNIA LIBRARY